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## CRYPTOCOCCOSIS

## Report of a Case and Experimental Studies

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AND

EDWARD L. ARTMAN, M.D.

LOS ANGELES

CRYPTOCOCCOSIS is a relatively rare disease, approximately 100 cases having been reported to date. It is characterized by invasion of the body by yeastlike organisms which have a special affinity for the lungs and central nervous system. Clinical manifestations are those of a subacute or chronic infection. Pathologically the response of the tissue is similar to that seen in other infectious granulomas.

The disease was first described by Frothingham,<sup>1</sup> who reported its occurrence in a horse. The first report of the disease in man is that of Stoddard and Cutler,<sup>2</sup> who published their monograph in 1916. There have been numerous reports since that time. Some of the more recent reviews include one by Reeves, Butt and Hammack<sup>3</sup> in 1941 and one by Voyles and Beck<sup>4</sup> in 1946.

The causative organism, *Cryptococcus hominis*, is widely distributed in nature as a saprophyte. It is a yeastlike organism which reproduces by budding only, without mycelial or endospore formation. In tissue the parasites are seen intracellularly surrounded by vacuoles.

Clinical manifestations vary with the site and extent of involvement. Systemic involvement includes, in order of decreasing frequency, the central nervous system, lungs, spleen, liver, kidneys, mesenteric nodes and ileum. The signs and symptoms are those of toxemia in association with those produced by destructive processes in involved organs. There may be a slight rise in temperature, with corresponding increase in pulse. Headache is the most common initial symptom along with various mental symptoms.

1. Frothingham, L.: A Tumor-Like Lesion in the Lung of a Horse Caused by *Torula*, J. M. Research 9:31, 1902.

2. Stoddard, J. L., and Cutler, E. C.: *Torula Infection in Man*, Monograph 6, Rockefeller Institute for Medical Research, 1916.

3. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: *Torula Infection of the Lungs and Central Nervous System*, Arch. Int. Med. 68:57-79 (July) 1941.

4. Voyles, G. Q., and Beck, E. M.: *Systemic Infection Due to Torula Histolytica*, Arch. Int. Med. 77:504-525 (May) 1946.

The pathologic lesion<sup>5</sup> consists of a small nodule from 0.5 to 0.8 mm. in diameter. The microscopic structure is that of miliary tubercles with absence of polymorphonuclear leukocytes. The organism occurs both intracellularly and extracellularly.

In the central nervous system there is chronic leptomeningitis, with thickening of the meninges and adhesions to the cortex. There is little exudation, but tubercles may be seen scattered through the brain substance. Two kinds of lesions are seen: one, a granulomatous perivascular lesion; the other, small nodules, tubercles or gelatinous cystlike structures scattered throughout the cerebral tissues. Microscopically these lesions have small spherical spaces filled with gelatinous material in which are embedded many cryptococci. There is insignificant cellular reaction about these lesions and only slight increase in glial tissue in the neighborhood of the focus. There are many monocytes and lymphocytes in and about the lesions, but in general the picture is that of solution of brain substance by the parasite without adequate inflammatory reparative processes.

In most cases of cryptococcosis the condition has been diagnosed and described at autopsy. Even when the diagnosis has been made before death the disease usually runs a subacute or chronic course which leads to inevitable death. To date no satisfactory therapeutic agent has been provided although numerous ones have been tried.<sup>6</sup>

We have been fortunate in being able to follow a patient previously reported on.<sup>8</sup> She has lived for nine years since the onset of symptoms. Five years have passed since the previous report. Sulfonamide compounds have provided the basis for her treatment throughout this period.

The experiments reported in this article were undertaken to evaluate the treatment given and to guide future therapy.

#### REPORT OF A CASE

A. C. L., a 14 year old white girl, first became ill in August 1937. At that time her symptoms consisted of headache, nausea, vomiting, failing vision, slight fever and a productive cough.

She was first examined at the Carmichael Hospital for Tropical Diseases at Calcutta, India, where neurologic examination was noncontributory and lumbar puncture revealed slightly increased pressure. Roentgenograms of her chest

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5. Jacobson, H. P.: *Fungous Disease*, Springfield, Ill., Charles C Thomas, Publisher, 1932, pp. 253-279. Gay, F. P.: *Agents of Disease and Host Resistance*, *ibid.*, 1935, pp. 1109-1151. Conant, N. F., and others: *Manual of Clinical Mycology*, Philadelphia, W. B. Saunders Company, 1945, pp. 111-125.

6. Marshall, M., and Teed, R. W.: *Torula Histolytica Meningo-Encephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy*, *J. A. M. A.* **120**:527-529 (Oct. 17) 1942. Tinney, W. S., and Schmidt, H. W.: *Torula Infection*, *M. Clin. North America* **28**:950-956 (July) 1944.

revealed empyema of the right interlobar area, which was explored surgically and found to consist mainly of fibrous tissue with signs of chronic inflammation. No organisms were recovered. A draining sinus persisted at the site of the operation.

In December 1937 the spinal fluid pressure was 290 mm. and the fluid contained many polymorphonuclear cells and gave a positive Wassermann reaction but yielded no organisms. The reaction to a Wassermann test of the blood was questionably positive. Roentgenograms of the skull revealed a beaten silvery appearance, with increased convolutional markings. Ophthalmoscopically, both optic disks were pale, particularly that of the right eye.

In February 1938 a craniotomy was performed in the right frontal area. The brain was found to be under increased intracranial pressure, but no abscess was found.

In April 1938 the patient entered the Hospital of the Good Samaritan in Los Angeles under the care of Dr. Robert Cunningham and Dr. Roy Hammack.

At this time the appearance was that of a pale, apathetic, emaciated white girl of about 15 years. A well healed craniotomy scar was evident, and the sinus in the chest was still draining. The optic disks had the appearance of primary atrophy. Besides constricted visual fields, no other neurologic changes were detected. The blood pressure was 120 systolic and 80 diastolic. Roentgenograms of the chest in June 1938 revealed an area of density, extending upward and outward from the right hilus, which occupied the anterior part of the chest and appeared to involve the interlobar fissure. A roentgenogram of the skull demonstrated the healed craniotomy wound as well as considerable accentuation of the convolutional markings. The hemoglobin content was 67 per cent, the red blood cell count 4,010,000 and the white blood cell count 7,100, with 65 per cent polymorphonuclear cells and 25 per cent lymphocytes. A Wassermann test of the blood gave a negative reaction. Lumbar puncture revealed a pressure of 200 mm., with 73 cells per cubic centimeter (predominantly polymorphonuclear cells) and 175 mg. of protein per hundred cubic centimeters. The reaction of the spinal fluid to a Wassermann test was negative. The colloidal gold curve was 5555554211. *Cryptococcus hominis* was observed on smear and grown on culture of the material drained from the sinus in the chest. The organism was also grown in a culture of the spinal fluid. After this the patient was discharged to her home. She was taking 15 grains (0.97 Gm.) of potassium iodide daily.

*Second Admission.*—The patient was admitted nine months later for reexamination. She felt stronger and had gained 17 pounds (7.7 Kg.). Headache was still present, and *C. hominis* was cultured from the spinal fluid. The lesion in the chest had decreased in size roentgenologically. She received a ten day course of sulfapyridine, during which time the blood sulfapyridine level ranged between 9 and 13 mg. per hundred cubic centimeters.

*Third Admission.*—The patient reentered the hospital in May 1939, and the only noteworthy change was an increase in strength. Organisms were still recoverable from the sinus in the chest and from the spinal fluid. A ten day course of sulfanilamide was started, a blood concentration of between 9 and 12 mg. per hundred cubic centimeters being maintained.

*Fourth Admission.*—By December 1939 she had gained 15 pounds (6.8 Kg.) and felt much improved. Roentgen examination showed further decrease of the lesion in the chest. Lumbar puncture showed a pressure of 200 mm., with 46 cells per cubic centimeter and 225 mg. of protein per hundred cubic centimeters. *Cryptococcus hominis* was again cultured from the spinal fluid. She was given undenatured Torula antigen (Kreuger) and has continued using 1.0 cc. twice weekly since that time.



*Fifth Admission.*—The patient had improved sufficiently to attend a school for the blind until September 1941, and in October she was readmitted complaining of headache and dizziness. The physical and neurologic condition was unchanged. The blood pressure was now 150 systolic and 100 diastolic. *Cryptococcus hominis* could no longer be cultured from the sinus in the chest but was recovered from the spinal fluid. Sulfadiazine was given for twelve days, with the blood concentration ranging between 10 and 13 mg. per hundred cubic centimeters. The patient left the hospital improved after two weeks.

*Sixth and Seventh Admissions.*—The sixth and seventh admissions cover the period from October 1943 to October 1944. On both occasions the patient was admitted because of signs and symptoms of increased intracranial pressure. The symptoms were alleviated by lumbar puncture and rest in bed. On neither occasion was *C. hominis* cultured from the spinal fluid, and no specific treatment was attempted.

*Eighth Admission.*—In July 1945 the patient was readmitted because of recurrence of headache and vomiting. Lumbar puncture demonstrated increased pressure, cells and protein. The colloidal gold curve was 133433210. *Cryptococcus hominis* was cultured from the spinal fluid. She was again started on sulfadiazine, and she continued to take the drug for a period of six weeks, during which time the blood sulfadiazine level was maintained between 7.8 and 10.9 mg. per hundred cubic centimeters.

*Ninth, Tenth and Eleventh Admissions.*—The ninth, tenth and eleventh admissions cover the period from October 1945 to February 1946. The patient was admitted for study and sulfadiazine therapy. The physical condition remained unchanged, and the blood pressure was 160 systolic and 100 diastolic. Neurologic examination now showed an increase of the deep tendon reflexes. The sinus in the chest remained dry. Lumbar puncture showed increased pressure, cells and protein. Culture of the spinal fluid did not reveal any cryptococci, nor did numerous cultures of the urine. Urinalysis showed only a trace of albumin. The blood sulfadiazine level was maintained at 14 to 17 mg. per hundred cubic centimeters on two occasions for two week periods of therapy.

*Twelfth Admission.*—The patient reentered the hospital in May 1946 for further study and treatment. There were no complaints, and the blood pressure was 160 systolic and 106 diastolic. Ophthalmoscopically, the picture of advanced optic atrophy was seen. A check of the visual fields showed the right eye to be entirely unreliable, and lack of central vision in the left eye made it impossible to outline the blindspot and adjacent blind areas. Electroencephalographic study showed a persistently abnormal wave pattern over both frontal and temporal lobes. The abnormality consisted of slow waves of 3 and 6 cycles per second combined with rapid waves of 17 to 19 cycles per second. The amplitude of these abnormal wave patterns often came close to or exceeded 100 microvolts. This type of abnormality was felt to be consistent with cortical irritation on account of pressure. There were no focal signs. The nonprotein nitrogen was 27 mg. per hundred cubic centimeters, urea clearance 73 per cent, albumin 5.2 Gm. and globulin 2.0 Gm. Culture of the urine did not reveal any cryptococci. The kidneys, ureter and bladder were normal.

The patient was started on another course of sulfadiazine therapy, but administration of the drug had to be discontinued on the fourth day on account of hematuria. Accordingly, sulfanilamide was tried, but this was soon withheld because of excessive nausea and vomiting. At no time was there any evidence of depression of the bone marrow from the use of either drug.

The patient was discharged to her home and is being followed in the outpatient department.

### EXPERIMENT

In order to evaluate various therapeutic agents in the treatment of cryptococcosis, the following experiments were performed: A preliminary study was made to determine the pathogenicity of the organism. A five month old culture of the patient's spinal fluid was used as the source for organisms. This was subcultured on plates of modified agar-plain agar with 5 per cent dextrose and 0.5 per cent tartaric acid. Culture plates were washed with sterile isotonic solution of sodium chloride to provide a suspension of cryptococcus organisms. Twenty million organisms thus obtained were inoculated intraperitoneally into white rats. Animals of this group were followed for fifty days. It was found that the organism being used produced only localized lesions in test animals. These lesions consisted of

TABLE 1.—*Length of Survival of Animals After Infection with Cryptococcosis*

Animal Group	Average Days of Survival After Infection
Preinfected and untreated.....	6.2
Healthy and untreated.....	11.4
Healthy and treated with sulfadiazine.....	28.9
Healthy and treated with penicillin.....	22.6
Healthy and treated with sulfadiazine and penicillin.....	22.1
Healthy and treated with streptomycin.....	28.0
Healthy and inoculated with antigen.....	13.1

TABLE 2.—*Pathologic Findings in Twenty-Five Animals at Postmortem Examination*

Peritonitis.....	52%
Visceral abscesses.....	24%
Abdominal lymphadenopathy.....	20%
Empyema.....	16%
Pericarditis.....	8%
Pneumonia.....	8%
Subcutaneous nodules.....	8%
Meningitis.....	4%

subcutaneous nodules, involvement of lymph nodes and omental masses. Only a negligible number of animals succumbed to the cryptococcal infection. Accordingly, a number of animals were killed. The involved tissues were macerated with a sterile mortar and pestle and cultured on dextrose-tartaric acid agar. Three serial passages through white rats were then performed. Organisms obtained from the final passage were used in later experiments. After the third serial animal passage culture plates were washed with sterile isotonic solution of sodium chloride. The suspension of *C. hominis* thus obtained contained 1.3 billion organisms per cubic centimeter. Animals in the experiment were inoculated intraperitoneally with 0.5 cc. of this suspension (650,000,000 organisms). The animals used were white rats weighing 150 to 200 Gm. These animals may be grouped as follows:

1. Five animals who had been infected in the preliminary experiment with 20,000,000 original organisms but who showed no clinical evidence of disease were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. These animals received no treatment.

Five healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. These animals received no treatment.

2. Ten healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment with sulfadiazine sodium in 0.1 cc. of sterile isotonic solution of sodium chloride subcutaneously every four hours was started and was continued for twelve days. From then until the eighteenth day they received 0.006 Gm. in 0.2 cc. of sodium chloride every six hours. Treatment was abandoned at that time and the animals observed.

3. Eight healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment with penicillin sodium was started. Each animal received subcutaneously 50 units of penicillin (285 units per kilogram) dissolved in 0.1 cc. of sterile isotonic solution of sodium chloride every four hours for twelve days. From then until the eighteenth day they received 100 units of penicillin in 0.2 cc. of sodium chloride every six hours. Treatment was then abandoned and the animals observed for further changes.

4. Eight healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment was started with penicillin and sulfadiazine in combination. Each animal received 0.003 Gm. of sulfadiazine sodium in 0.1 cc. of isotonic solution of sodium chloride plus 50 units of penicillin sodium in 0.1 cc. of sodium chloride as two separate subcutaneous injections every four hours for twelve days. From then until the eighteenth day they received 0.006 Gm. of sulfadiazine sodium in 0.2 cc. of sodium chloride plus 100 units of penicillin sodium in 0.2 cc. of sodium chloride subcutaneously every six hours. Treatment then was abandoned and the animals observed for further changes.

5. Ten healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment was started with streptomycin. Each animal received 950 units of streptomycin sulfate (approximately 5,590 units per kilogram) in 0.1 cc. of sterile isotonic solution of sodium chloride subcutaneously every four hours for twelve days. From then until the eighteenth day each animal received 1,900 units of streptomycin sulfate in 0.2 cc. of sterile isotonic solution of sodium chloride every six hours. Treatment was then abandoned and the animals observed for further changes.

6. Eight healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. These animals received by subcutaneous injection 0.1 cc. of standard cryptococcus antigen (Kreuger) which had been diluted 1:60 with sodium chloride on the fourth, sixth and eighth days after infection. They were observed for further changes.

#### COMMENT

The results of the animal experiments conducted would indicate that sulfadiazine or streptomycin will prolong life expectancy in cryptococcosis. Penicillin afforded slight advantage, and there was no benefit noted in combining penicillin and sulfadiazine. It might be of value at a later date to determine if any advantage would accrue from combining sulfadiazine and streptomycin. Another factor of importance but unfortunately not covered by the present experiments is that of fluid balance. The amount of isotonic solution of sodium chloride used to dissolve the drugs employed would approximate 500 cc. daily

for the adult weighing 70 kilograms. This may be an important factor in prolonging life.

Animals which had been preinfected lived no longer than the control group. Animals untreated save for administration of vaccine lived no longer than the control group. These results might be taken to indicate that there is but slight tendency to form protective antibodies against the organism.

As regards the course of the disease in the patient discussed, she has long passed the life expectancy for persons afflicted with this disease. The lesion in her chest has definitely improved in the past several years, as evidenced by decrease in its size and decrease in amount of secretion. No organism has been recovered from the sinus in her chest for over five years. Changes in the central nervous system have

Group	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	64	
1a		o		o	o	o																									
1b		o		o					o			o																			
2					o	o		o		o	o	o			o			o												o	
3				o	o			o	o	o	o											o			o						
4		o								o	o	o	o		o	o									o						
5								o		o	o	o		o	o		o	o	o					o							
6				o	o	o	o	o											o												

Days of survival after infection. (Marks refer to individual animals.)

not been as progressive as one might expect them to be if the disease process were active. In the past three years culture of the spinal fluid has yielded cryptococci on only one occasion, which was a year ago.

It is of interest to note the development of hypertension in this patient. We believe that it is accounted for best on a basis of internal hydrocephalus, with increased intracranial pressure.

The role of sulfonamide compounds in this patient's disease is difficult to evaluate. We believe, however, that the course has been greatly modified by use of the drug.

#### SUMMARY

1. Animals previously infected with the cryptococcus and clinically appearing well gave no sign of having developed antibody protection against that organism.

Animals treated with sulfadiazine had their life expectancy increased from 11.4 to 28.9 days.

Animals treated with penicillin had their life expectancy increased from 11.4 to 22.6 days.

No advantage accrued when penicillin and sulfadiazine were used in combination.

Animals treated with streptomycin had their life expectancy increased from 11.4 to 28.0 days.

Vaccination as employed in this experiment did not appreciably alter the life expectancy of the animals used.

2. The course of the cryptococcic infection in the patient reported on would seem to have been altered by sulfonamide therapy.

# COMPLETE ATRIOVENTRICULAR BLOCK IN DIPHTHERITIC MYOCARDITIS

Report of a Case with Serial Electrocardiographic Tracings

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REVIEW OF THE ENGLISH LITERATURE, 1901 TO 1946

UNTIL recently, partial atrioventricular block in diphtheria has been recognized rarely and detailed serial studies of complete atrioventricular block in diphtheria have been scarce. It was difficult to ascertain from the literature the first reported cases of heart block of any degree, because undoubtedly some occurred which were unrecognized for want of technologic apparatus. White and Smith reviewed 946 cases of diphtheria in 1904 studied at the Boston City Hospital, and in 3 of these pulse rates "to 30 or even 20" were present; these undoubtedly were cases of complete heart block, but electrocardiographic technics were not available to the authors.

*First and Second Degree Atrioventricular Block.*—As Stecher noted, at least 2 instances of partial heart block in diphtheria have been reported before 1938, 1 by Hume in 1913 and 1 by Hecht, cited by Marvin, in 1924. Since 1938, Burkhardt and others and Neubauer have reported a total of 36 cases of partial heart block in diphtheria. The absence of reported cases of this lesion prior to that time probably was due to the fact that they were not recognized, since only by means of the electrocardiogram can the diagnosis of partial heart block be confirmed.

*Complete Atrioventricular Block.*—Sprague and White described a case, first observed in 1907, in which high grade heart block was due primarily to tonsillar diphtheria. Smith in 1921 observed no instances of low grade heart block but 10 instances of complete heart block in 242 consecutive cases of diphtheria. In 1937 Begg wrote: "A characteristic of diphtheritic lesions of the main bundle of His is that complete atrioventricular dissociation appears usually without pre-

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liminary changes in the P-R interval." This seems to be a phenomenon unique in myocarditis caused by *Corynebacterium diphtheriae*. In other cases of complete heart block the condition commonly progresses through the lesser degrees first. Begg's series of cases of severe faucial diphtheria comprised 100, in none of which was first or second degree heart block demonstrable. He observed that the usual sequence was "some abnormality in the ventricular portion of the tracing and then, suddenly, complete dissociation."

In 1938 Burkhardt, Eggleston and Smith reported on 140 cases, gathered over a period of one and one-half years, of toxic diphtheria. In 28 of these there were graphic changes in the electrocardiogram. In 17 cases conduction changes developed between the fifth and the thirteenth day of illness. Atrioventricular dissociation was manifested in 11 of these,

TABLE 1.—*Reported Cases of Diphtheritic Heart Block*

Authors	Year	Total Number of Cases	Number of Cases of Heart Block	
			Incomplete	Complete
Sprague and White.....	1907	1	0	1
Hume.....	1913	1	1	0
Jones and White.....	1915	2	0	2
Parkinson.....	1915	1	0	1
Smith.....	1921	242	0	10
Hecht.....	1924	1	1	0
Stecher.....	1928	19	0	19
Burkhardt and others (28 of 140 showed electrocardiographic changes).....	1938	17	6	11
Neubauer.....	1943	44	30	14
Givhan and Mahon.....	1945	10	1	0
Stimson.....	1946	1	0	1

and all 11 were fatal. Autopsies were performed in 7 cases, and Burkhardt and his co-authors felt that "there was a rough parallelism between the conductivity as shown by the electrocardiograph and the microscopic changes in the myocardium. Many cases showing atrioventricular dissociation presented a terminal picture of ventricular tachycardia."

#### HYPERTOXIC TONSILLOPHARYNGEAL DIPHThERIA

Our case <sup>1</sup> was one of fatal hypertoxic tonsillopharyngeal diphtheria occurring in a 17 year old white youth, in whom myocardial damage was manifested four days after the onset of the illness. Detailed serial electrocardiographic study was undertaken in an attempt to observe the progress of heart block in this disease. The major electrocardiographic features developing during the course of the illness were as follows:

1. The clinical and therapeutic aspects are published in detail in Walker, W.; Massey, F., and Mostofi, K.: Streptomycin-Resistant Diphtheria, J. A. M. A. 135:771 (Nov. 22) 1947.

(1) intraventricular block; (2) complete atrioventricular heart block with a progressively decreasing ratio of ventricular to auricular contractions; (3) shifting of the cardiac axis to the right; (4) terminal increased intraventricular block; (5) progressive diminution in amplitude of QRS complexes, and (6) appearance of what appeared to be interpolated premature auricular beats. The electrocardiographic tracing of June 3 showed intraventricular block (QRS measuring 0.12 second) but no impaired atrioventricular conduction (P-R interval, 0.16 second). Because of technical difficulties at this time, only lead I was obtainable, and the single tracing is not reproduced in this paper for that reason. The cardiac rate was 96 per minute. On the following day complete atrioventricular block developed, giving rise to a tracing manifesting a complex arrhythmia. A detailed inspection of the records obtained



Fig. 1.—Electrocardiogram of June 4, 1946. The auricular rate is 102 per minute, and the ventricular rate is 68 per minute. Complete atrioventricular block is present.

affords an excellent opportunity to study the progressive involvement by the diphtheritic infection of the cardiac conduction system and the myocardium.

*Progressive Electrocardiographic Changes.*—There are two features of the electrocardiogram of June 4 (fig. 1) which identify it as revealing a complete atrioventricular block. The first of these is the fact that the ventricular complexes occur at regular intervals. This distinguishes the condition immediately from partial atrioventricular block with irregular ventricular response. The second diagnostic feature is the fact that the P waves are not fixed in their relationship to the ventricular complexes, which differentiates this from a partial atrioventricular block



with regular ventricular response. The auricular rate is 102 per minute. The ventricular rate is 68 per minute.

Irregularity of ventricular beating does occur in complete atrio-ventricular block in these circumstances: (1) when there is a shifting of the idioventricular pacemaker, (2) in the presence of premature ventricular systoles and (3) when there is arrhythmia of a single idioventricular pacemaker. The first of these is demonstrated in the tracing of June 9 (fig. 5) and the second in the tracing of June 5 (fig. 2). The record of June 5 also is identifiable as showing complete atrioventricular block by the fact that the P waves are not fixed in their position in the ventricular premature contractions. The presence of intraventricular block may be assumed, since the QRS complexes measured 0.12 second

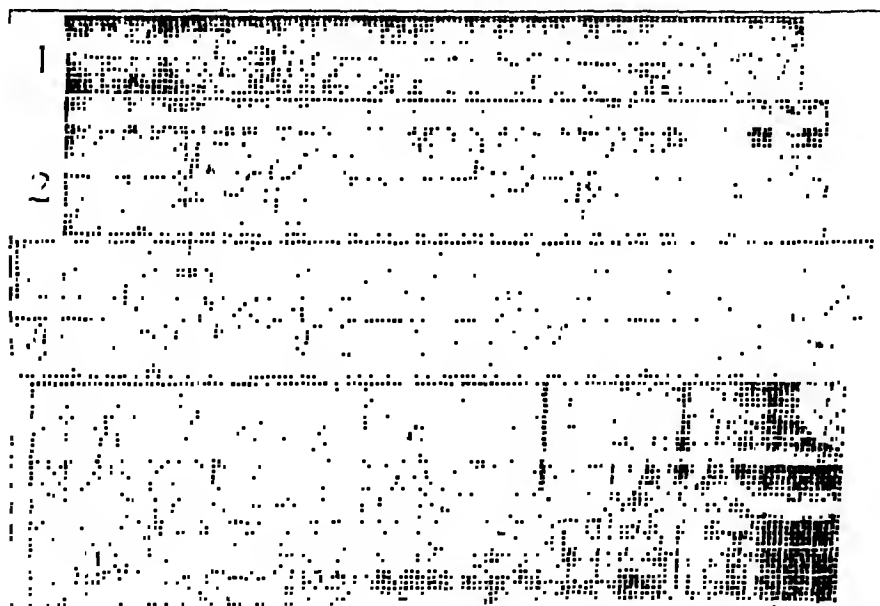


Fig. 2.—Electrocardiogram of June 5, 1946. Complete atrioventricular block complicated by the appearance of premature ventricular contractions. The auricular rate is 104 per minute, and the ventricular rate is 52 per minute.

on June 3, prior to the appearance of atrioventricular block. Ventricular ectopic contractions from several foci at times produce a coupled rhythm. The auricular rate is 104 per minute. The ventricular rate is 52 per minute.

In the tracings of June 6 (fig. 3) the features of complete atrio-ventricular block are again apparent, with occasional ventricular ectopic contractions. On the assumption that the idioventricular pacemaker has remained stationary between June 4 and 6, this tracing shows a pronounced shifting of the cardiac axis to the right. Also, there has been elevation of the S-T segment in lead I and inversion of the T waves with depression of the S-T segments in leads II and III.

Tracings taken later on the same day showed a mechanism basically similar to that in these electrocardiograms.

On June 7 (fig. 4) the ventricular rate decreased from 50 to 42 per minute. The auricular rate was 96 per minute. Elevation of the S-T

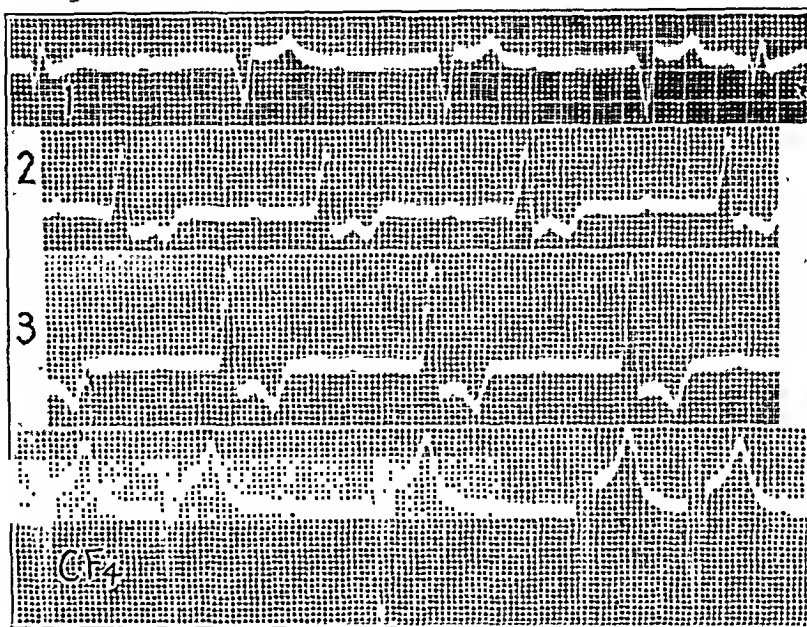


Fig. 3.—Electrocardiogram of June 6, 1946. Complete atrioventricular block with notable deviations in the S-T segment. The auricular rate is 98 per minute, and the ventricular rate is 50 per minute.

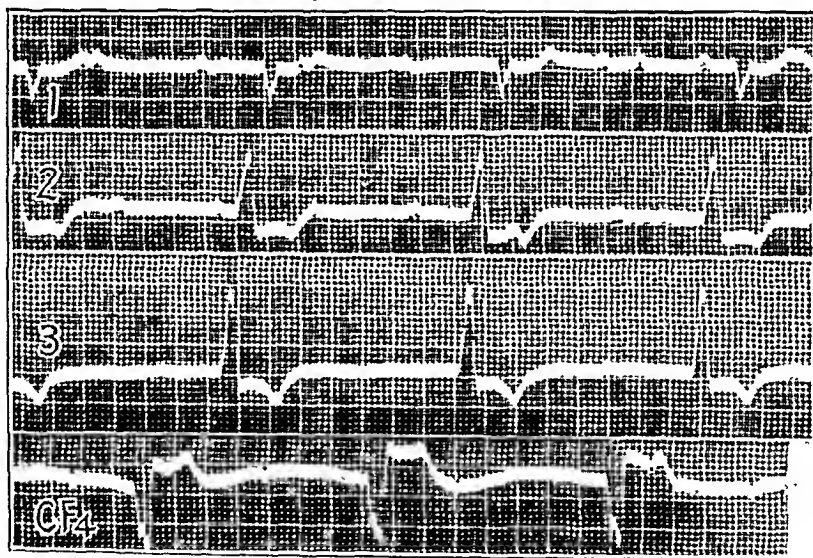


Fig. 4.—Electrocardiogram of June 7, 1946. Auricular rate is decreased to 96 per minute and the ventricular rate reduced to 42 per minute. Marked depression of the S-T segments in leads II and III is seen, with elevation of the S-T segment in lead CF<sub>4</sub>. The QRS interval measures 0.12 second.

segment in lead I had disappeared, but depression of the S-T segments persisted in leads II and III, with comparable elevation in lead CF<sub>4</sub>.

The QRS interval measured 0.12 second. What appeared to be an interpolated auricular premature beat was noted in lead I (between the third and fourth ventricular complexes).

By June 9 (fig. 5) the ventricular rate had slowed remarkably to 34 per minute while the auricular rate remained relatively constant at 98. Since the tracing of June 7 the changes in the S-T segment and in the T waves in leads II and III essentially had disappeared. The elevated S-T segment in  $CF_4$  was not as extreme as in the tracings of June 7 (fig. 5). This tracing is notable for the presence of two idioventricular pacemakers. This produced a coupled rhythm shown best in leads III and  $CF_4$ .

Decrease of the ventricular rate to 26 per minute, with an auricular rate averaging 104 at 10:45 p. m. is the outstanding feature of the record of June 11 (fig. 6). The QRS interval is widened to 0.16 second.

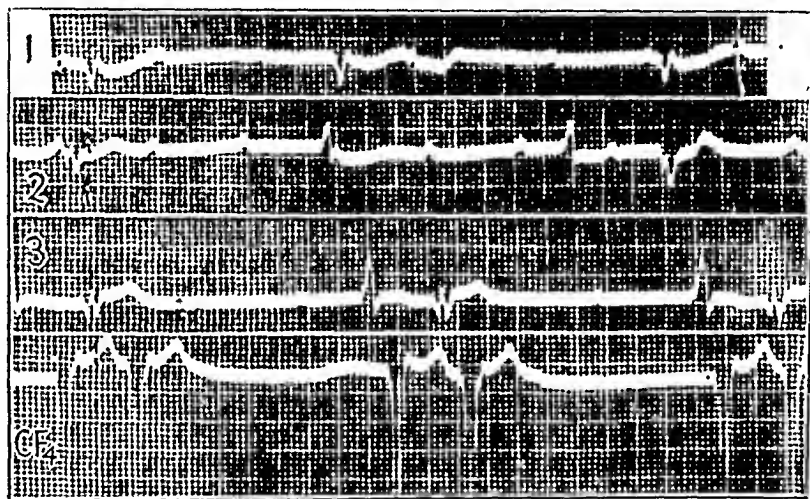


Fig. 5.—Electrocardiogram of June 9, 1946. The auricular rate is 98 per minute, while the ventricular rate has slowed still further to 34 per minute. Coupling is manifested.

Further return to normalcy of the S-T segments is present. There has been some decrease in voltage of the QRS complexes. In lead  $CF_4$  two ventricular contractions occur in such rapid succession that they nearly superimpose their QRS inscriptions. What appear to be interpolated auricular premature beats again are seen in leads II and III of this tracing. This was the last electrocardiogram, obtained just prior to death, which occurred six hours later.

#### OBSERVATIONS AT AUTOPSY

*Gross Changes.*—Pertinent findings at necropsy included 1,000 cc. of clear, straw-colored fluid in the peritoneal cavity, with the liver extending 9 cm. below the xiphoid in the midline and 1 cm. below the

costal margin in the right anterior axillary line. Each pleural cavity contained 400 cc. of clear, straw-colored fluid.

The heart weighed 420 Gm. and was found lying transversely in situ, with the right border formed almost entirely of the enlarged right atrium. Anteriorly, the cardiac mass was made up of the hypertrophied, dilated right ventricle. Posteriorly, a small left ventricle was found. The left atrium was small.

Numerous petechiae were seen on the epicardium, but it was smooth and glistening as was the endocardium, which showed no hemorrhage. Measurement of the wall of the left ventricle showed it to be 1.8 cm. thick; the wall of the right ventricle was 0.4 cm. thick. The myocardium had a mottled, purplish brown appearance, and it was soft. The valves were unremarkable, and the coronary vessels were normal.

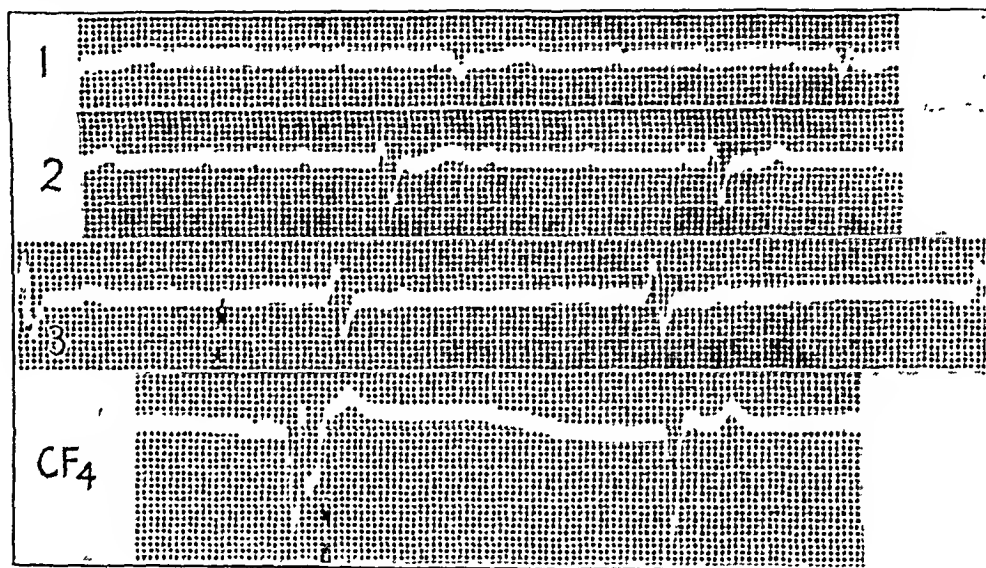


Fig. 6.—Electrocardiogram of June 11, 1946—just prior to the patient's death. The auricular rate at this time was 104 per minute but the ventricular rate has dropped still further to 26 per minute. Intraventricular block, with a QRS interval of 0.16 second, is seen.

*Histopathologic Process.*—Extensive myocarditis was apparent, the myocardial fibers, specially those of the ventricle, showing edema and notable degenerative changes. These alterations included cloudy swelling, fragmentation and vacuolization, hyaline degeneration, loss of nuclei and complete destruction of many muscle fibers to a degree at which only debris filled the sarcolemma. Other myocardial fibers had been replaced entirely by loose fibrous tissue. Although widespread, these changes were patchy, leaving isolated groups of muscle fibers unaffected by the process. Frequently associated with the necrotic areas and occasionally independent of them were infiltrations of inflammatory cells including monocytes, plasma cells, lymphocytes and some polymorphonuclear

leukocytes and eosinophils. Macrophages and multinucleated giant cells were also seen. In a few areas, especially in the wall of the left ventricle and in the periatrionodular nodal region, the focal accumulation of inflammatory cells was so dense that it simulated abscess formation.

Section of the periatrionodular nodal region particularly showed advanced degeneration of the muscle fibers in the midst of intense cellular infiltration. The sinoatrial node was less involved. Atrial pathologic change was not as great.



Fig. 7.—Gross specimen of the heart and pericardium, showing numerous petechial hemorrhages.

#### COMMENT

While it is obvious that the highly specialized function of the myocardial fibers (atrial and ventricular), that is, contractility, was tremendously impaired, it is also plausible to assume that the conducting tissues lost much of their ability to transmit stimuli with normal rapidity. As a result of progressive inflammatory-toxic changes, irreparable damage was wrought.

As borne out by histopathologic examination, the atrial musculature was less severely impaired than the ventricular, which possibly is a contributory factor for the phenomenon of the progressively diminishing ventricular rate despite a relatively constant atrial rate. Conduction itself was hampered considerably, and this was the prime basis for the advent of complete heart block and prior intraventricular block.

Clinically, right ventricular failure was evident two days before death, but pathologic enlargement of the right side of the heart occurred and was reflected in the electrocardiographic pattern before this time. Hepatic congestion and ascites were demonstrated clinically, and the diagnosis was confirmed at autopsy. Peripheral edema was not present.

### SUMMARY

1. A survey of the English literature on the subject of heart block in myocarditis caused by *Corynebacterium diphtheriae* is presented which

TABLE 2.—*Progressively Decreasing Ratio of Ventricular to Auricular Contractions*

Date	Auricular Rate	Ventricular Rate
June 3.....	96	96
June 4.....	102	68
June 5.....	104	52
June 6.....	98	50
June 7.....	96	42
June 9.....	98	34
June 11.....	104	26

indicates that partial atrioventricular block was rarely recognized until recently and that serial electrocardiographic studies of complete atrioventricular block are few.

2. A detailed analysis is made of a complex arrhythmia with complete atrioventricular block and a progressively decreasing ventricular rate occurring in a case of hypertoxic tonsillopharyngeal diphtheria.

3. Observations at autopsy indicated that in a general way the lesions produced by the disease were reflected directly in the serial electrocardiographic studies.

Colonel Albert H. Robinson, Medical Corps, Tacoma, Washington, and Lowell L. Lane, M.D., Philadelphia, assisted in the preparation of this paper.

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# LIPOMELANOTIC RETICULAR HYPERPLASIA OF LYMPH NODES

Report of Six Cases

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CHICAGO

THE ASSOCIATION of a peculiar type of hyperplasia of lymph nodes with chronic dermatitis was first pointed out by Pautrier and Woringer<sup>1</sup> in 1937. They reported 11 cases in which there were dermatitis and lymphadenopathy. In 4 instances lymph nodes were removed and showed a peculiar type of hyperplasia. The dermatitis varied in type and degree but was usually erythematous, desquamative and associated with pruritus. The lymph node hyperplasia was characterized by the multiplication of reticular cells, the presence of intracellular fat and melanin pigment and slight infiltration with eosinophils. In 1941 Soloff<sup>2</sup> reported a case in which there were similar changes in the inguinal lymph nodes in a patient who died of disseminated miliary tuberculosis.

It should be noted that in many of the reported cases there was widespread lymphadenopathy, which led to a clinical diagnosis of lymphoblastoma.

In this paper 6 cases of chronic dermatitis, pruritus and lymphadenopathy are reported, and the gross and microscopic features of lipomelanotic reticular hyperplasia of lymph nodes are described.

## REPORT OF CASES

CASE 1.—P. F., a 59 year old Negro, was first admitted to the hospital on July 24, 1943, because of a cutaneous eruption and pruritus.

For the previous ten years he had had an eruption on the exposed parts of his body during the months from April to August. The affected skin showed

From the Institute of Pathology, Western Reserve University, Cleveland, Ohio, and the department of pathology of Northwestern University and Wesley Memorial Hospital.

1. Pautrier, L. M., and Woringer, F.: Contribution à l'étude de l'histopsiologie cutanée; à propos d'un aspect histo-pathologique nouveau du ganglion lymphatique: la réticulose lipo-mélanique accompagnant certaines dermatoses généralisées; les échanges entre la peau et le ganglion, *Ann. de dermat. et syph.* 8:256-273, 1937.

2. Soloff, L. A.: Lipomelanotic Reticular Hyperplasia of Lymph Nodes: Report of a Case, *J. Lab. & Clin. Med.* 27 (pt. 1):343-346, 1941.



increased pigmentation, scaling and thickening, and there was an accompanying pruritus of moderate degree. During the fall and winter the skin gradually regained its normal color and texture. Several years after he first noticed the cutaneous lesions a series of scratch tests were done to determine the presence or absence of sensitivity to many common flowers. Several of these gave positive reactions. During the year preceding the admission to the hospital he worked on a small farm and did not come in contact with any of the flowers to which he was said to be sensitive. Early in May he noticed the usual eruption appearing on his face, arms and hands. Shortly before he came to the hospital the eruption spread to involve his entire body.

Physical examination on admission revealed that the temperature was 37.3 C. (99 F.), the pulse rate 80, the respirations 20 and the blood pressure 150 systolic and 100 diastolic. The patient was well developed and well nourished. The skin of the face, neck and arms showed a notable increase in pigmentation, thickening, scaling and edema. Similar changes were present but to a less degree on the trunk and the lower part of the legs. The liver was palpable 3 fingerbreadths below the right costal margin. There was slight pitting edema of the lower part of the legs. The rest of the examination revealed nothing abnormal.

Laboratory examination at the time of admission showed a trace of albumin in the urine, 4,800,000 red blood cells, with a hemoglobin content of 95 per cent (Sahli), and 12,200 white blood cells (50 per cent neutrophils, 48 per cent lymphocytes and 2 per cent monocytes). The reaction to the Kline test was negative.

On his second day in the hospital a small area of skin on the posterior aspect of the thorax was exposed for one and a half minutes to a mercury vapor lamp at a distance of 30 inches (76 cm.). In twenty-four hours this site was erythematous, and in forty-eight hours the skin was edematous and small papules were evident. This reaction was evident for several days, after which pigmentation increased in amount.

The cutaneous lesions improved markedly when treated with calamine ointment and potassium permanganate baths. The patient was discharged on the ninth day in the hospital. The clinical diagnosis was chronic actinic dermatitis due to sensitivity to ultraviolet rays.

He was readmitted to the hospital on Sept. 5, 1944, with a similar pruritic cutaneous eruption. Since his previous admission he had noticed multiple nodules in the groins, left forearm and right knee.

Physical examination on his second admission revealed that the temperature was 37.6 C. (99.6 F.), the pulse rate 88, the respirations 14 and the blood pressure 190 systolic and 100 diastolic. The skin of the arms, axillas, abdomen and thighs was markedly indurated. The axillary and inguinal lymph nodes were moderately enlarged, firm and nontender. In the dermis of the left forearm and of the outer aspect of the right knee there were firm nodules up to 3 cm. in diameter.

On the second admission the urine was normal. The red blood cells numbered 3,860,000, with a hemoglobin content (Sahli) of 84 per cent, and the white blood cells 12,600 (49 per cent neutrophils, 35 per cent lymphocytes, 2 per cent monocytes and 14 per cent eosinophils).

On his second day in the hospital a biopsy of a nodule on the left forearm was done. The surgical specimen consisted of a piece of colored skin and subcutaneous tissue with a maximum measurement of 2 cm. The epidermis was distinctly increased in thickness and showed diffuse hyperkeratinization, patchy parakeratosis and diffuse acanthosis. The dermis was increased in thickness,

fibrotic and infiltrated with many lymphocytes, large mononuclear cells and a few eosinophils. The subcutaneous tissue showed similar fibrósis and cellular infiltration (fig. 1).

On his twelfth day in the hospital a lymph node in the left inguinal area was removed. The surgical specimen consisted of an enlarged lymph node with a maximum diameter of 2.5 cm. This was slightly softer than usual and sectioned with decreased resistance, and it had a bulging pale yellow cut surface. Microscopic examination revealed a few lymph follicles, which in most instances had secondary centers. These follicles were farther apart than usual because of the



Fig. 1 (case 1).—Slight hyperplasia of epidermis. Infiltration of upper part of dermis with lymphocytes, large mononuclear cells and eosinophils. Hematoxylin and eosin;  $\times 225$ .

large number of reticular cells in the cortex (fig. 2). Similar reticular cells of large size with pale eosinophilic and vacuolated cytoplasm were abundant in the medulla. Some of these large reticular cells contained sudanotropic droplets, and in many there was granular dark brown pigment, which because of its solubility in hydrogen peroxide was identified as melanin (fig. 3). Eosinophils were present in moderate number. The diagnosis was lipomelanotic reticular hyperplasia of lymph nodes.

The skin was treated with two courses of superficial roentgen irradiation (75 r), which resulted in considerable relief of the pruritus. A 5 per cent solution of ammoniated mercury ointment was also used. At the time of discharge, on the eighteenth day in the hospital the skin was much softer and the itching was slight.

CASE 2.—B. H., a 48 year old white woman, was admitted to the hospital on Dec. 6, 1944, with the complaint of "marked itching of the skin." Her illness began eight months before, when she noticed a purple macular rash in the right groin. This was treated with roentgen irradiation and disappeared. Similar macular lesions appeared in the left groin, and they disappeared with similar

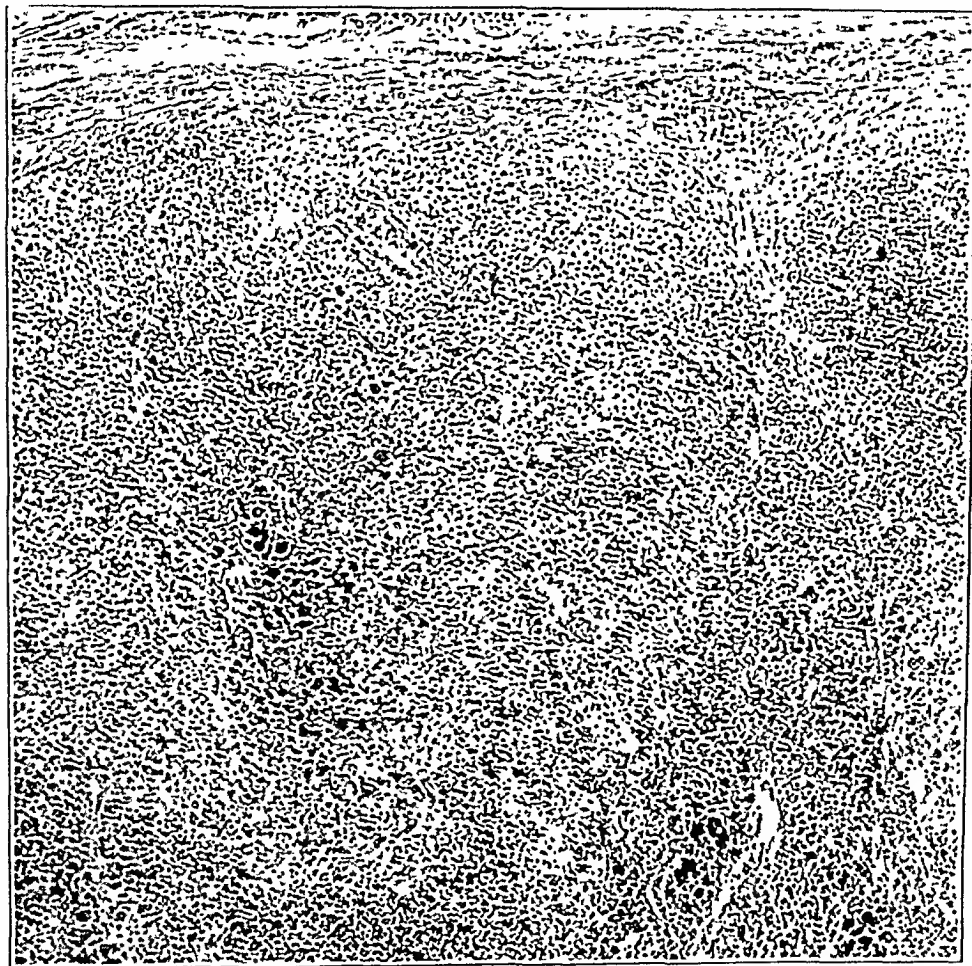


Fig. 2 (case 1).—Portion of cortex of lymph node with many large reticular cells and no lymph follicles. Pigment (melanin) in reticular cells. Hematoxylin and eosin;  $\times 100$ .

treatment. A short time later lesions appeared on the scalp, neck, thorax and abdomen. Vesicles also developed, and in July 1944 pruritus became pronounced. At this time she was treated in the dispensary. The history revealed a loss of 30 pounds (13.6 Kg.) in weight during the previous six months. A diagnosis of seborrheic dermatitis was made.

Physical examination on admission revealed a temperature of 37.4 C. (99.3 F.), a pulse rate of 88, respirations 24 and a blood pressure of 150 systolic and 105

diastolic. The patient was poorly developed and obviously undernourished, and she appeared to be chronically ill. The skin was dry, with poor turgor and patchy glistening and scaly areas. Vesicles were present in both inguinal regions, and there were fissures behind the ears. The hair was decreased in amount over the vertex of the scalp. The cervical axillary, epitrochlear and inguinal lymph nodes were increased in size and were firm and nontender. The remainder of the examination was noncontributory.

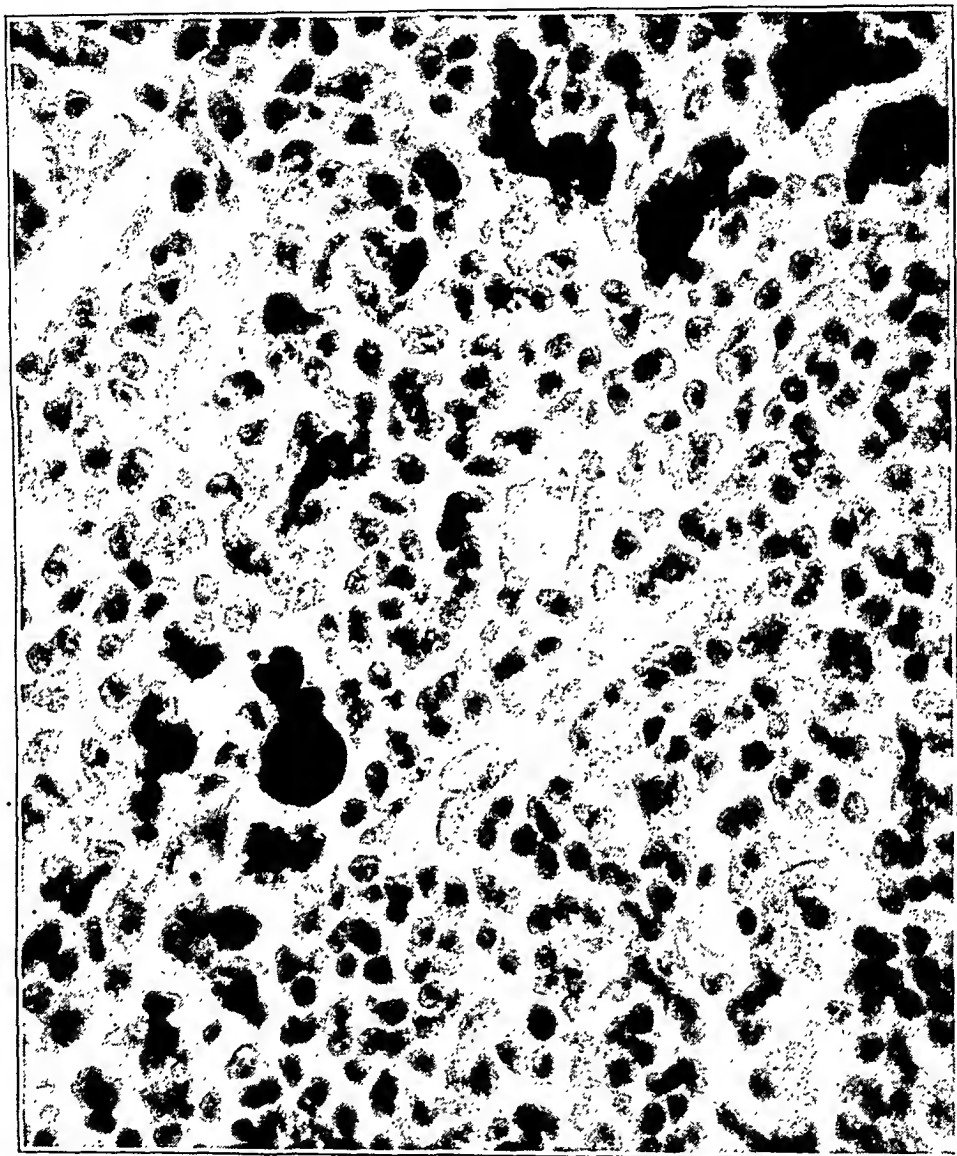


Fig. 3 (case 1).—Reticular cells containing pigment (melanin) in substance of lymph node. Hematoxylin and eosin;  $\times 750$ .

Laboratory examination on admission showed the urine to be normal. The red blood cell count was 3,230,000, with a hemoglobin content (Sahli) of 74 per cent, and the white blood cell count 6,350 (63 per cent neutrophils, 22 per cent lymphocytes, 7 per cent monocytes and 7 per cent eosinophils). There was a negative reaction to the Kline test.

*Course in the Hospital.*—She was given potassium permanganate baths (1:10,000) twice daily. Cottonseed oil was also used on the skin, and zinc stearate powder was applied to "weeping" areas. On many occasions she exhibited

depressive symptoms. She was examined by a neuropsychiatrist, who made a diagnosis of "psychoneurosis with reaction depression."

The white blood cell count varied between 5,650 and 7,800. The basal metabolic rate was +12 per cent.

On her fifth day in the hospital a biopsy was performed, the tissue consisting of a small elliptic piece of white skin. The epidermis was moderately increased in thickness and showed slight parakeratosis and acanthosis. The upper part of the dermis was infiltrated with a moderate number of lymphocytes and large mononuclear cells and an occasional eosinophil. The diagnosis was chronic dermatitis.

On her seventh day in the hospital two of the inguinal lymph nodes were removed. At this time the clinical diagnosis was lymphoblastoma, probably Hodgkin's disease. The surgical specimen consisted of two lymph nodes with maximum measurements of 1 and 1.5 cm. Microscopic examination (fig. 4) revealed the architectural patterns of the lymph nodes to be preserved. The lymph follicles in the cortex were slightly enlarged, and many had distinct secondary centers. Eosinophils were present in moderate numbers throughout the cortical and medullary portions. In the medullary portions there were numerous large mononuclear cells with faintly eosinophilic and, in many instances, vacuolated cytoplasm. Some of these cells contained brown pigment that was soluble in hydrogen peroxide, and many contained sudanotropic droplets. The diagnosis was "lipomelanotic reticular hyperplasia of lymph nodes."

The patient was discharged on the twenty-fifth day in the hospital. At this time she showed moderate improvement, and the clinical diagnosis was seborrheic dermatitis of the scalp and widespread exfoliative dermatitis.

CASE 3.—F. S., a white man aged 56 years, was admitted to the hospital on Jan. 2, 1945. He was a tire maker in a rubber plant and had been working with synthetic rubber for two years. He had been in good health until five months prior to hospitalization, when an erythematous papular eruption developed on the skin of both legs. This was patchy in distribution and was diagnosed as eczema by his private physician. When the eruption became widespread he was referred to a dermatologist. At this time the history revealed slight loss of weight, increasing irritability, excessive perspiration and tremor of the hands. His basal metabolic rate was +50, but his pulse was normal. After treatment of the cutaneous lesions with roentgen rays (three or four times), an ointment and one of the sulfanamide compounds, there was no improvement. The pruritus became severe.

Physical examination at the time of admission revealed a temperature of 37.5 C. (99.5 F.), a pulse rate of 82, a respiratory rate of 25 and a blood pressure of 140 systolic and 90 diastolic. He was normally developed and slightly undernourished. There was widespread erythema, thickening, scaling and excoriation of the skin. The thyroid was not enlarged. The axillary and inguinal lymph nodes on the right and left sides were enlarged (measuring 1 to 3 cm. in maximum diameter), firm, discrete, freely movable and slightly tender. The cervical lymph nodes were similarly enlarged, though to a lesser degree. The thorax was not unusual except for a moderate increase in the anteroposterior diameter. The heart was normal. There was a fine tremor of the hands. Small anal fissures and internal hemorrhoids were noted.

Laboratory examination at the time of admission showed the urine to be normal. The red blood cell count was 5,100,000, with 98 per cent hemoglobin (Sahli), and the white blood cell count 10,300 (79 per cent neutrophils, 11 per cent

lymphocytes, 5 per cent monocytes, 5 per cent eosinophils and 1 per cent basophils). The reaction to the Kline test was negative, and the plasma cholesterol level was 198 mg. per hundred cubic centimeters.

*Course in the Hospital.*—The cutaneous eruption was treated with boric acid ointment (1:5,000), potassium permanganate baths, 5 per cent bismuth tribromphenate, 10 per cent liquid carbonic detergents and irradiation. On two occasions the trunk was treated with 50 r, and on one occasion the hands and arms were treated with 50 r.

On the eleventh day in the hospital his temperature suddenly rose to 39 C. (102.2 F.). At this time there developed hoarseness, a productive cough and



Fig. 4 (case 2).—Abundance of large reticular cells in the cortex of a lymph node, some containing melanin. Hematoxylin and eosin;  $\times 250$ .

signs of bilateral bronchopneumonia. He was given a total of 400,000 units of penicillin over a period of three days. The signs and symptoms of the respiratory infection disappeared in six days, and it was thought that at the same time there was a distinct improvement in the cutaneous eruption. He was therefore given an additional 500,000 units of penicillin over a period of five days, but there was no further change in the cutaneous lesions.

While he was in the hospital many laboratory examinations were done. At the time of the respiratory infection his white blood cell count was elevated to 27,550 and the urine contained a small amount of albumin and a few white blood cells. A glucose tolerance test gave a normal reaction. His basal metabolic

rate was constantly elevated, varying between +23 and +65. The total plasma protein content was 5.04 Gm., with albumin 3.00 Gm. and globulin 2.04 Gm. per hundred cubic centimeters.

On his third day in the hospital a biopsy of the skin of the right forearm showed moderate hyperplasia of the epidermis, with hyperkeratinization, parakeratosis and acanthosis. There was also moderate cellular infiltration of the upper part of the dermis. The infiltrate consisted of many lymphocytic and large mononuclear cells and a few eosinophils.

On his seventh day in the hospital one of the lymph nodes in the left inguinal area was removed. The surgical specimen consisted of a lymph node 1.8 cm. in maximum measurement. Its consistency and resistance to section were slightly reduced. The cut surface was soft and pale yellow. Microscopic examination showed relatively few small, widely separated lymph follicles. Large reticular cells with pale eosinophilic and vacuolated cytoplasm were numerous in both the cortex and the medulla (fig. 5). Intracellular dark brown pigment (fig. 6), soluble in hydrogen peroxide, was abundant, and a few eosinophils were present. These changes are typical of lipomelanotic reticular hyperplasia of lymph nodes.

The cutaneous eruption improved slightly, and he gained some weight before being discharged on his fifty-third day in the hospital.

CASE 4.—M. P., a 56 year old white woman, was first admitted to the hospital on Jan. 10, 1945, because of a rash of two years' duration.

Her illness began two years prior to her hospitalization while she was working in a tailor shop. She first noticed itching of the skin of the hands, forearms and face. Shortly afterward pruritic erythematous papules appeared, and these sites became roughened and scaly. After the onset of her illness she was examined by her private physician, who made a diagnosis of monocytic leukemia with cutaneous involvement. Her cutaneous lesions were treated symptomatically with numerous ointments, and she was also given sixteen roentgen ray treatments (75 r each) over a two year period.

Physical examination at the time of admission revealed a temperature of 37.4 C. (99.3 F.), a pulse rate of 80, a respiratory rate of 18 and a blood pressure of 146 systolic and 90 diastolic. The patient was well developed and moderately obese. The skin showed widespread erythema and thickening and numerous excoriations. The pharynx was slightly reddened, and the tonsillar tissue was slightly increased in amount. The axillary and inguinal lymph nodes were considerably increased in size and were firm, discrete and nontender. The largest node was in the right axilla and measured 5 cm. in diameter. A systolic murmur was heard in the third right intercostal space. This was transmitted downward but not into the neck. There was also a systolic murmur at the apex, and the second aortic sound was accentuated. No cardiac enlargement could be demonstrated by percussion. No abdominal organs were palpable. There was slight pitting edema of the lower extremities.

At the time of admission the urine contained albumin (0 to 1 plus) and 10 to 40 white blood cells per high power field in sediment. The red blood cell count was 4,960,000, with a hemoglobin content of 100 per cent (Sahli), and a white blood cell count of 12,350 (54 per cent neutrophils, 12.5 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils, 20.5 per cent abnormal [monocytoid] cells and 2 per cent blastocytes). The reaction to the Kline test was negative.

*Course in the Hospital.*—The skin was treated with tannic acid, witch hazel and boric acid ointment. The axillas and the right groin were also treated with roentgen radiation (200 r).



Additional laboratory examinations revealed a white cell count of 10,300, with a differential count of 45.5 per cent neutrophils, 12 per cent lymphocytes, 7.5 per cent monocytes, 0.5 per cent eosinophils and 34.5 per cent abnormal cells. The abnormal cells were identified as large monocytoïd cells. "Their nuclei were made up of chromatin in granular strands, frequently showing segmentation. A few of the cells had two nuclei. The cytoplasm of the abnormal cells was slate grayish blue, nontransparent and frequently vacuolated. Some of the cells had pseudopods. The erythrocytes showed slight variation in size and shape. Platelets

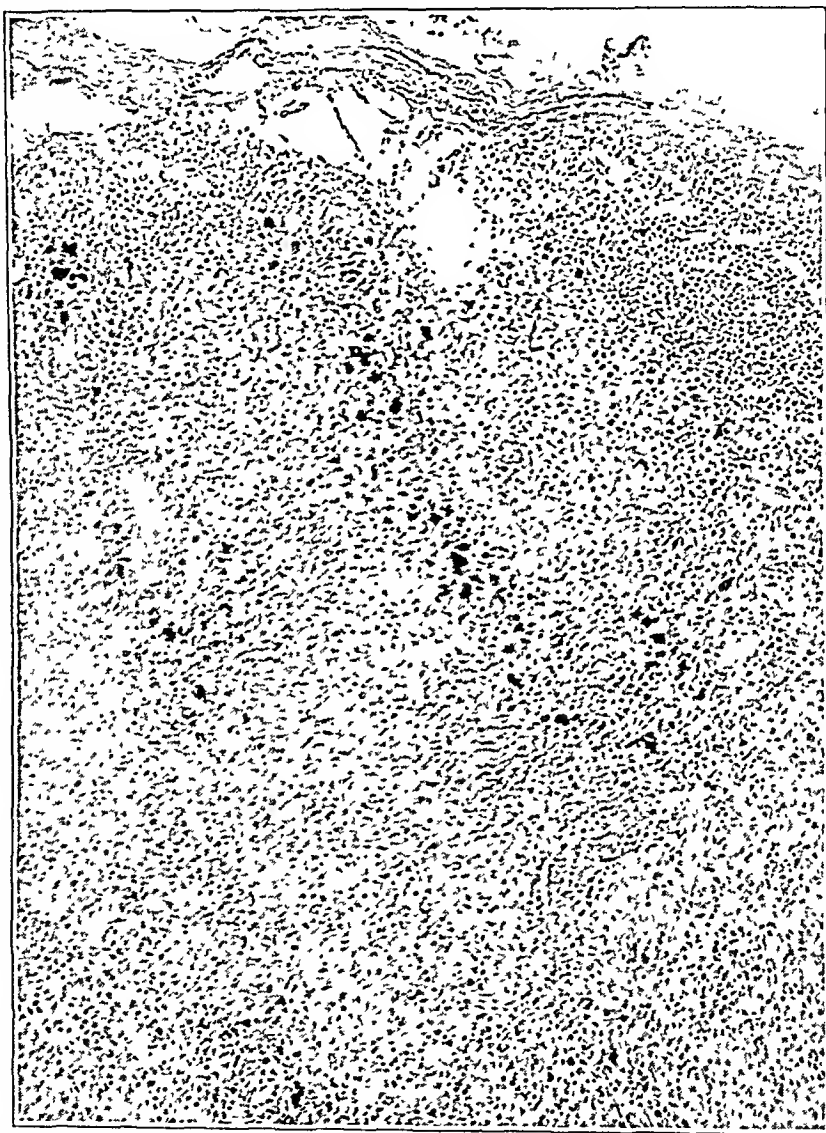


Fig. 5 (case 3).—Hyperplasia of reticular cells in the cortex of a lymph node. Many of these cells contain melanin. No lymph follicles are present. Hematoxylin and eosin;  $\times 100$ .

were normal in number, but a few large forms were seen. Blood smears stained by the supravital method showed the structure of these cells to be more like the structure of the lymphocytic than that of the monocytic series."

Aspiration of the sternal marrow on the first day in the hospital showed normal marrow cells, the only abnormality being a slight increase in the number of eosinophils.



A clinical diagnosis of monocytic reticuloendotheliosis or Schilling type of monocytic leukemia was made.

On her second day in the hospital a biopsy of the skin of the left arm showed the epidermis to be the seat of hyperkeratinization, parakeratosis and acanthosis. The upper third of the dermis was infiltrated with many cells including lymphocytes and large mononuclear cells. Some of the latter had atypical deeply chromatic nuclei of irregular shape. Kingsley and reticulin stains revealed no cells of the granulocyte type and no increase in the amount of reticulin. Because of distinct nuclear pleomorphism of the cells in the dermis (fig. 8 *A*), the original diagnosis of chronic dermatitis was revised to lymphoblastoma "consistent with

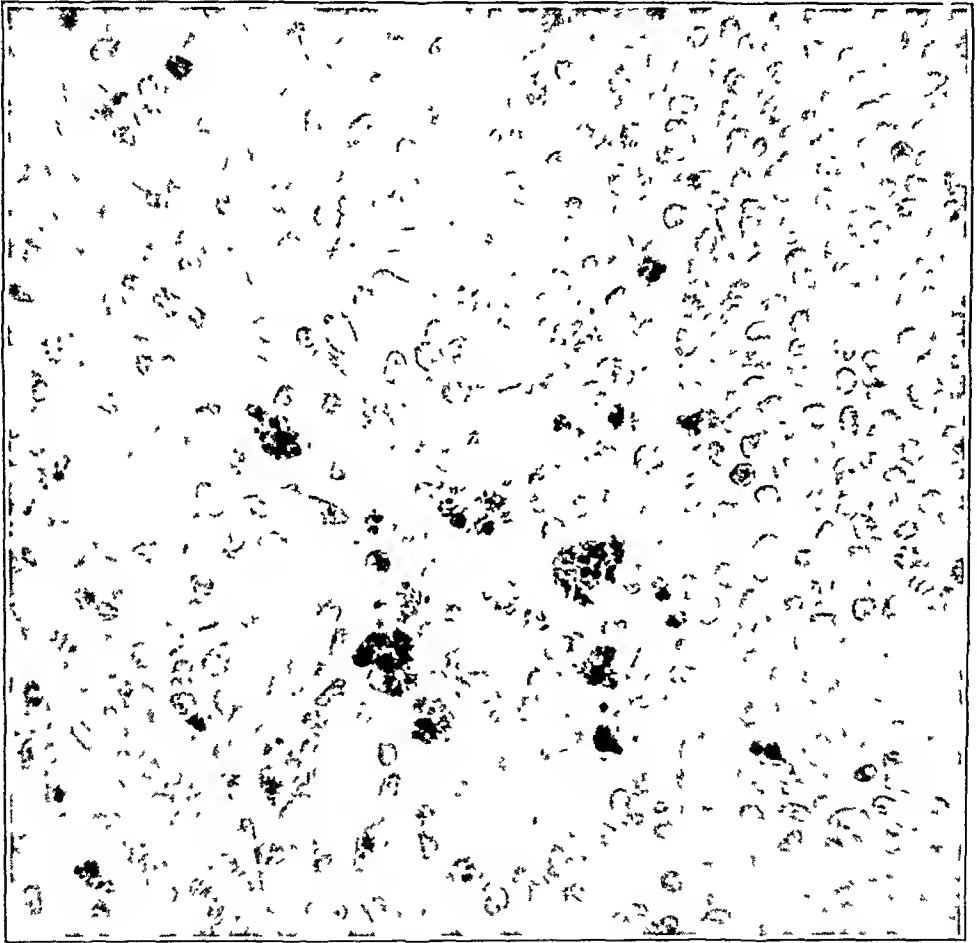


Fig. 6 (case 3).—Large reticular cells are present in the cortex of a lymph node; some of these contain melanin. Hematoxylin and eosin;  $\times 660$ .

a diagnosis of monocytic leukemia." It should be noted that no eosinophils were present in the dermis.

On her seventh day in the hospital one of the lymph nodes in the left inguinal area was removed. The surgical specimen consisted of a lymph node 2.2 cm. in maximum measurement. Its capsule was intact, and its consistency and resistance to section were reduced. The bulging cross section was pinkish yellow. The microscopic features were those of lipomelanotic reticular hyperplasia and leukemic infiltration. There was moderate alteration in the normal architectural pattern. Lymph follicles were few in number and widely separated. Large mono-

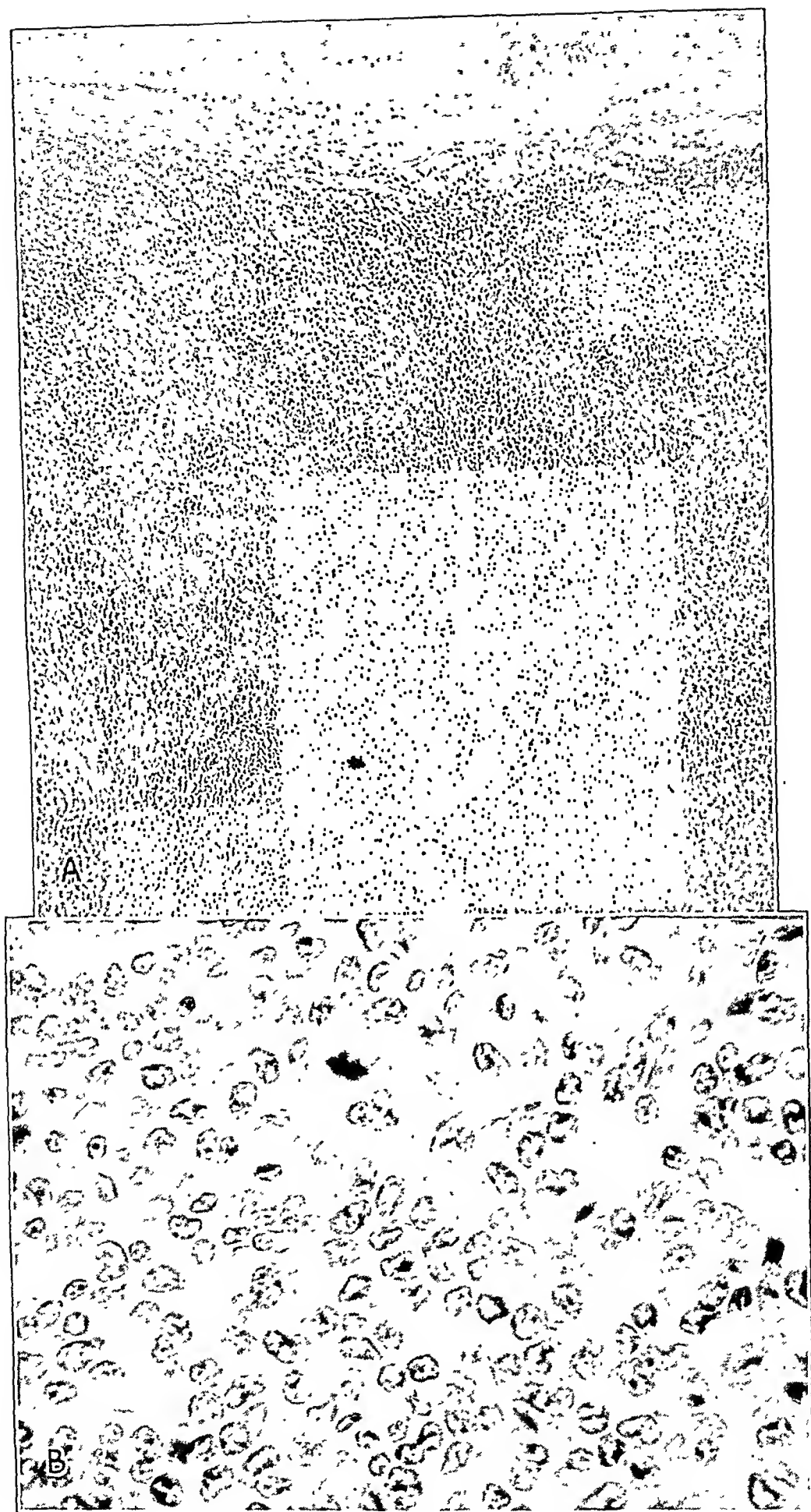


Fig. 7 (case 4).—*A*, hyperplasia of reticular cells in the cortex of the lymph node. No lymph follicles are present. Hematoxylin and eosin;  $\times 100$ . *B*, cells of large size with indented nuclei (cells of monocyte series) are present in the medulla of a lymph node. Hematoxylin and eosin;  $\times 850$ .

nuclear (reticular) cells with faintly eosinophilic cytoplasm were abundant throughout the cortex (fig. 7A). A considerable amount of sudanotropic material was present in the large reticular cells, but melanin was not abundant and eosinophils were few in number. On the first examination the presence of atypical cells was not noted. With more careful scrutiny, many cells of unusual type were noted, particularly in the medulla. These were large cells with indented nuclei of variable size and homogeneous, moderately eosinophilic nonvacuolated cytoplasm (fig. 7B). Lymphocytes were scarce.

The patient was discharged on the sixteenth day in the hospital after having shown decided improvement.

She was again hospitalized on Sept. 29, 1945, because of "strangling attacks and shortness of breath." In February 1945 she noticed loss of hearing of the left ear. Subsequently she became excited, maniacal and hysterical. She was kept in a sanatorium for four weeks, during which time she had dyspnea without relation to exertion, position or meals, but her excitement decreased. After leaving the sanatorium she became more nervous and began taking sedatives and stimulants. On August 16, while sitting in a chair, she suddenly became dyspneic, excited and flushed. After this time such attacks became more pronounced and frequent. During the attacks she was flaccid and could not talk.

At the time of the second admission the urine contained albumin (2 plus) and 50 to 70 white blood cells and a few casts in the sediment. The red blood cell count was 4,190,000, with a hemoglobin content of 80 per cent (Sahli), and a white blood cell count of 10,500 (65 per cent neutrophils, 7 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils and 23 per cent atypical monocytoïd cells).

*Course in the Hospital.*—The temperature varied between 37.3 and 38 C. (99 to 100.4 F.). Roentgenograms of the chest showed no enlargement of the lymph nodes and no change since the previous examination in January 1945. With roentgen ray treatment the superficial lymph nodes decreased moderately in size. The pruritus was controlled by means of massage with olive oil and mineral oil and sedation. The patient was discharged to a nursing home on the eighth day in the hospital. The clinical diagnosis was Schilling's monocytic leukemia, arteriosclerotic heart disease and attacks of anxiety hysteria.

She remained in the nursing home for the next nine months. Her condition gradually became worse, and she died on May 25, 1946.

The autopsy revealed monocytic leukosis (Schilling type), with involvement of the thymus, pericardium, lungs, liver (1,910 Gm.), spleen (700 Gm.), adrenals, kidneys, lymph nodes and bone marrow. The immediate cause of death was bilateral bronchopneumonia.

The microscopic changes in the involved organs were different from those in the skin and lymph nodes examined sixteen months prior to the patient's death. The large mononuclear cells showed more variation in size and shape, distinct nuclear pleomorphism and acidophilic homogeneous cytoplasm. Mononuclear cells containing sudanotropic material, melanin and eosinophils were not present.

CASE 5.—S. N., a white woman aged 64 years, was admitted to the hospital on April 26, 1945, with the complaint of "itchy skin." Her illness began in the winter of 1941, when her skin became red, rough and scaly. The condition gradually became worse up to the time of her hospitalization.

In the past she had always been "nervous and high strung." She had frequently been troubled with "nervous indigestion," and in 1937 she had had an attack of "mucous colitis." She had also noted moderate exertional dyspnea,

slight swelling of the legs, substernal pain, palpitation and nocturia. She had undergone thyroidectomy in 1942.

Physical examination at the time of admission revealed a temperature of 37.7 C. (99.8 F.), a pulse rate of 88, a respiratory rate of 22 and a blood pressure of 170 systolic and 70 diastolic. She was well developed and well nourished and appeared apprehensive but not seriously ill. The skin of the trunk and extremities was red and rough. The cutaneous changes were symmetrically distributed and were most pronounced on the lateral aspects of the extremities, where scaling and excoriations were particularly notable. The lymph nodes in the right and left axillary and inguinal areas were moderately enlarged, firm and nontender; The thorax was normal except for a slight increase in the anteroposterior diameter. The heart was not enlarged on percussion, but a systolic murmur was heard at the apex. All reflexes were markedly hyperactive.

Laboratory tests on the day of admission gave the following results: The urine was normal except for the presence of 10 to 15 white blood cells and occasional granular casts per high power field. The red blood cell count was 3,870,000, with a hemoglobin content of 82 per cent (Sahli), and the white blood cell count 10,150 (69 per cent neutrophils, 27 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils).

*Course in the Hospital.*—Additional laboratory examinations revealed fasting blood sugar contents of 79, 102 and 110 mg. per hundred cubic centimeters and curves for glucose tolerance like those of a patient with a slight degree of diabetes mellitus. The basal metabolic rate was +5, and there was slight enlargement of the heart on roentgenologic examination. The white blood cell count varied between 8,800 and 14,300, with a differential count similar to that at the time of admission to the hospital except that there were many monocytes of the Schilling type.

On the fourth day in the hospital an elevated cutaneous nodule was excised. Microscopic examination revealed moderate hyperplasia of the epidermis, with moderate hyperkeratinization and appreciable acanthosis. In the deeper part of the dermis there were typical nevus cells, and in the upper part there were small and large mononuclear cells. The large mononuclear cells showed distinct abnormality of nuclei, but the changes were not considered to be sufficient in degree to warrant a positive diagnosis of leukemia.

On the eighth day in the hospital one of the lymph nodes in the right inguinal area was removed. The surgical specimen consisted of a lymph node with a diameter of 1.2 cm. Its consistency and its resistance to section were average. The cross section was pale pink. The microscopic sections showed a normal architectural pattern, with a few lymph follicles. Large reticular cells with abundant pale eosinophilic cytoplasm were numerous in the medulla and in the inner part of the cortex. Some of the reticular cells contained sudanotropic droplets, and in a few there was dark brown pigment that was soluble in hydrogen peroxide (fig. 8B). In addition there were many cells with indented nuclei suggestive of monocytes, particularly in the medulla.

While the patient was in the hospital her skin was kept oiled with coal tar, ammoniated mercury and petrolatum containing cod liver oil. She was discharged on the twenty-fifth day in the hospital slightly improved. The clinical diagnosis was Schilling's monocytic leukemia and diabetes mellitus.

CASE 6.—J. B., a Negro of 52 years of age, was referred to the dispensary because of varicose veins of the legs. His history indicated that he had had varicose veins for ten years, an ulcer on the right leg for eight months and an ulcer of the left leg for two months. The ulcer on the right leg had healed on

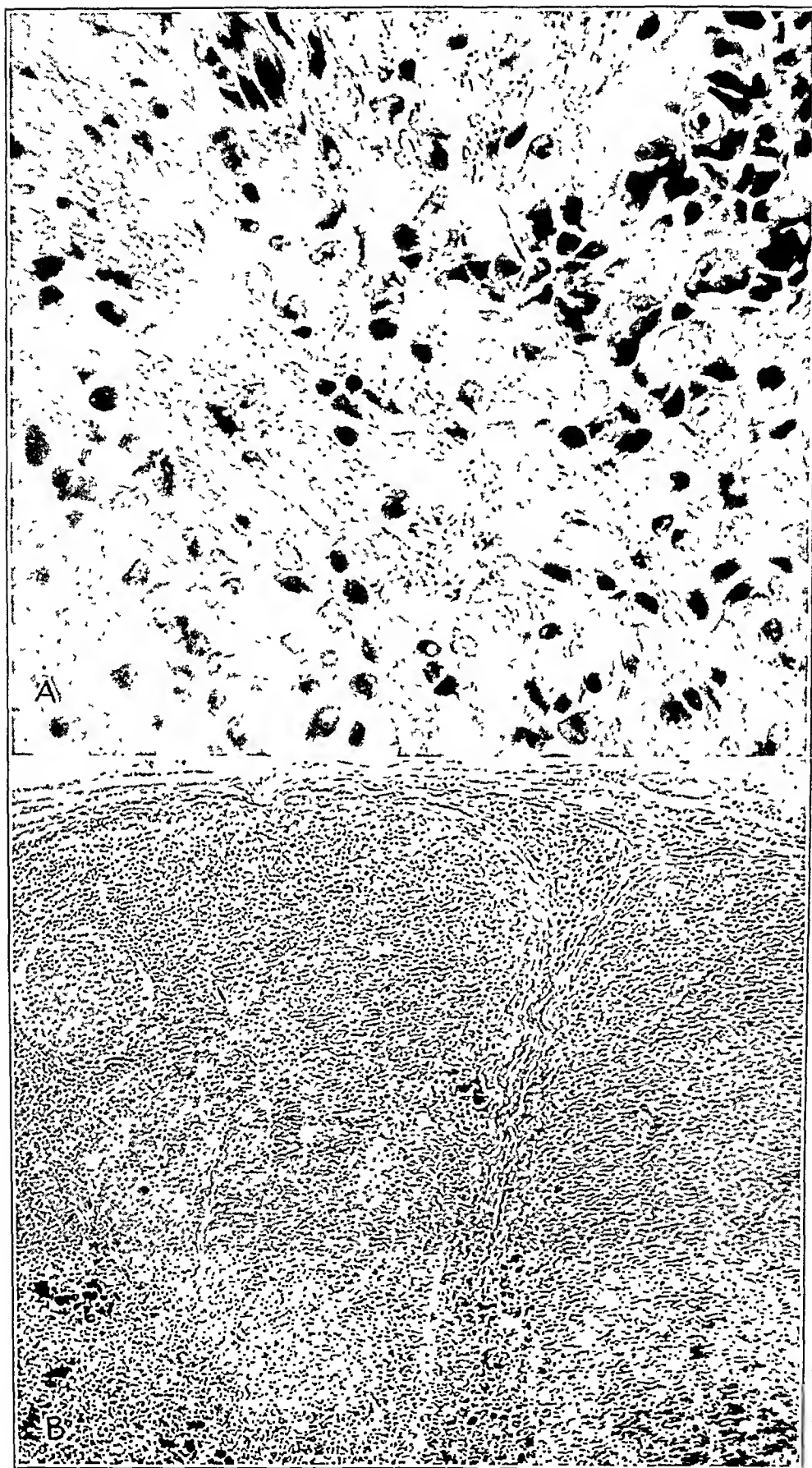


Fig. 8.—*A* (case 4), cells in the dermis show distinct variation in size and have large and irregularly shaped nuclei. The cellular infiltration is due to monocytic leukosis. Hematoxylin and eosin;  $\times 660$ . *B* (case 5), increase of reticular cells and deposition of melanin in the periphery of a lymph node. One lymph follicle with a secondary center is present. Hematoxylin and eosin;  $\times 100$ .

several occasions after periods of rest. Physical examination revealed an enlarged and tortuous right long saphenous vein, a patent deep venous system on the right, an ulcer measuring 3 inches (7.6 cm.) in diameter on the medial aspect of the right leg, palpable thrombosed veins of the left lesser saphenous system, a patent deep venous system on the left, an ulcer half an inch (1 cm.) in diameter over the left medial malleolus, moderately enlarged nontender inguinal lymph nodes and a small firm nodule medial to and below the right patella.

On Sept. 9, 1946, ligations of the saphenous veins were done high and low on the right side; the nodule below the right patella and a lymph node in the right inguinal area were removed. The nodule was cut into at the time of operation and contained clear colorless gelatinous material.

The surgical specimen included the cyst wall and lymph node. The former was made up of dense fibrous connective tissue in which there were a few lymphocytes and large mononuclear cells. The lymph node had a maximum measurement of 1.3 cm. It was average in consistency and sectioned with the usual resistance. The cross section was pale pink. Microscopic examination revealed focal fibrosis and normal lymph follicles. Reticular cells of large size with large amounts of faintly eosinophilic cytoplasm were present in moderately increased numbers in the medulla. A few of these cells contained sudanotropic droplets, and many contained brown pigment that was identified as melanin by its solubility in hydrogen peroxide. Eosinophils were few. The diagnosis was slight chronic inflammation of a cyst wall and slight lipomelanotic reticular hyperplasia of a lymph node.

The patient was last seen on Sept. 24, 1946, at which time the surgical wounds were well healed. The ulcers were cleaned and dressed. He did not return to the dispensary as instructed.

#### COMMENT

The cases recorded in this paper are illustrative of a distinct clinico-pathologic entity which, although not generally recognized, is probably not uncommon. The clinical manifestations include dermatitis, usually with severe pruritus and enlargement of lymph nodes. The cutaneous lesions vary in degree and distribution. There is usually considerable erythema, scaling and excoriation. A typical exfoliative dermatitis may develop. The lymphadenopathy may be widespread but is in most instances particularly notable in the axillary and inguinal regions. The enlarged lymph nodes are characteristically firm, discrete and nontender. Other manifestations of lymphoblastoma such as persistent leukocytosis, abnormal white cells in the circulating blood, anemia, and splenomegaly are absent in the uncomplicated cases.

Biopsies of skin reveal chronic dermatitis without a characteristic microscopic picture. The epidermis may be slightly thickened. The cellular infiltration of the dermis is made up of lymphocytes, large mononuclear cells and eosinophils. In some instances an occasional mononuclear cell contains melanin, but in none is there noteworthy cellular pleomorphism.

The lymph nodes are grossly enlarged and slightly softer than usual, and they have intact capsules. There is reduced resistance to section,

and they have bulging pale yellow cross sections. The yellow color is suggestive of the presence of fat, and rarely brown mottling due to melanin pigmentation is noted.<sup>2</sup> The microscopic picture of the lymph nodes is characteristic. The normal architectural pattern may be slightly altered, but it is never completely obscured. The predominant cell is the large mononuclear (reticular) cell with abundant faintly acidophilic cytoplasm that is frequently vacuolated. The cytoplasmic vacuolization is due to sudanotropic material, which is readily demonstrated with Sudan stains. These large cells are particularly conspicuous in the cortexes, where, when abundant, they alter the normal architectural pattern. The lymph follicles may be slightly enlarged, with distinct secondary centers, but they usually appear to be decreased in number because of wide separation by the large reticular cells in the cortical region. A varying number of large mononuclear cells contain granular dark brown pigment, which is identified as melanin by the lack of a reaction to potassium ferrocyanide and hydrochloric acid and by its solubility in hydrogen peroxide. Eosinophils, although not numerous, are always present. Plasma cells may be noted, but they are usually few in number. Fibrosis and giant cells are not part of the microscopic picture. Cellular pleomorphism is usually not striking. In this respect the case reported by Soloff,<sup>2</sup> in which there was appreciable cellular pleomorphism in the lymph node, is atypical.

The dermatitis is considered to be primary and the changes in the lymph nodes secondary. The inflammation of the skin causes hyperplasia of the draining lymph nodes. The scratching induced by pruritus probably brings about increased formation and liberation of melanin from cells of the epidermis. Such pigment would then be transported to regional lymph nodes and phagocytosed by reticular cells. Thus the amount of melanin pigmentation of the lymph node is dependent on the duration and severity of the pruritic dermatitis. The sudanotropic material in the reticular cells is probably secondary to excessive amounts of fat entering the cutaneous lymphatic vessels as a result of scratching and injury.

In normal lymph nodes or in those which are the seat of ordinary follicular or reticular hyperplasia, melanin and fat are usually absent or are present in exceedingly small amounts. That small amounts of melanin may be present in otherwise normal lymph nodes was demonstrated by Keye.<sup>3</sup> For comparison with the lymph nodes in the cases reported in this paper, forty lymph nodes which were the seat of reticular and follicular hyperplasia were examined and stained with Sudan

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3. Keye, K. R.: Ueber die natürliche Abwanderung des Pigments aus der Haut in die Lymphdrüsen bei Pferden, *Centralbl. f. allg. Path. u. path. Anat.* 34:57-60, 1923.

IV. In some there were a few reticular cells that contained sudanotropic droplets; but in none was the amount of sudanotropic material as great as in the lymph nodes which were the seat of lipomelanotic reticular hyperplasia.

The mechanism of development of lipomelanotic reticular hyperplasia of lymph nodes is such that it can theoretically occur in any condition of inflammation and itching of the skin. Thus the presence in lymph nodes of changes characteristic of lipomelanotic reticular hyperplasia does not of necessity preclude the concomitant existence of a lymphoblastoma. Thus in cases 4 and 5 the changes in the blood, skin and lymph nodes were consistent with a diagnosis of monocytic leukosis of Schilling type. It should be noted that in both instances the changes in superficial lymph nodes were those of lipomelanotic reticular hyperplasia as well as of monocytic leukemia. At the time of autopsy the microscopic changes in the thymus, liver, spleen, lymph nodes, kidneys and bone marrow in case 4 were different from those in lipomelanotic reticular hyperplasia. In these organs the large mononuclear cells showed considerable variations in size and shape, distinct nuclear pleomorphism and moderately acidophilic, homogeneous, nonvacuolated cytoplasm without sudanotropic droplets. None of the lymph nodes contained melanin or eosinophils. From an anatomic standpoint, therefore, the microscopic features of Schilling's monocytic leukosis and those of lipomelanotic reticular hyperplasia of lymph nodes are easily distinguished. Nevertheless, patients with the Schilling type of monocytic leukosis<sup>4</sup> usually have a relatively long course of illness, and cutaneous lesions with pruritus may develop. It is essential, therefore, that the possibility of the existence of this type of monocytic leukemia be kept in mind in the treatment of patients who have the clinicopathologic entity of pruritic dermatitis and lipomelanotic reticular hyperplasia of lymph nodes.

#### SUMMARY

Chronic dermatitis, particularly when accompanied with pruritus, may result in a characteristic type of hyperplasia of lymph nodes. The lymph nodes are usually moderately enlarged, discrete, firm and non-tender. On gross examination they frequently have a yellow tinge and occasionally show dark brown mottling. The microscopic features include slight distortion of normal architectural pattern, severe hyperplasia of reticular cells, which contain melanin and sudanotropic droplets, and infiltration with eosinophils. The secondary centers of the lymph follicles are sometimes evident, but the notable proliferation of

4. Montgomery, H., and Watkins, C. H.: Monocytic Leukemia: Cutaneous Manifestations of the Naegeli and Schilling Types; Hemocytologic Differentiation, *Arch. Int. Med.* 60:51-63 (July) 1937.



reticular cells is in the pulp of the lymph nodes. Six cases of dermatitis and this type of hyperplasia of lymph nodes are reported. In many instances, because of the prominence of the lymphadenopathy an incorrect clinical diagnosis of lymphoblastoma may be made. A diagnosis of lipomelanotic reticular hyperplasia of lymph nodes does not preclude the possibility of the concomitant existence of a lymphoblastoma. Thus in 2 of the cases reported in this paper there were changes in the blood and tissues that warranted the diagnosis of Schilling's monocytic leukemia. Lipomelanotic reticular hyperplasia of lymph nodes is a benign lesion that is secondary to chronic pruritic dermatitis. Although it may be associated with leukemia, Hodgkin's disease or lymphosarcoma it has no direct relationship to them.

## ADENOMAS OF THE ADRENAL CORTEX

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ADENOMAS of the adrenal cortex are reported in 1.45 to 33 per cent of all autopsies,<sup>1</sup> and they have been considered to be of significance in hypertension and diabetes mellitus.<sup>2</sup> This study represents an attempt to determine the incidence of adenomas of the adrenal cortex and to ascertain whether they occur more often in patients with hypertensive cardiovascular disease, cardiac enlargement, diabetes mellitus or gonadal changes.

For this study, any roughly spherical nodule with a diameter greater than 3 mm. budding from an edge of the gland or into the medulla was considered to be an adenoma of the adrenal cortex. The tumors contained variable proportions of vacuolated and eosinophilic cells resembling those of the adrenal cortex. The histologic architecture, however, was distinctly different from that of normal adrenal cortex. None of the nodules showed evidence of malignant change. Detailed reports of cytologic and histologic characteristics have been made previously.<sup>3</sup>

### OBSERVATIONS

Reports on 9,866 consecutive autopsies from January 1932 to March 1943 were examined. In the reports on 7,437 a gross and

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From the Mallory Institute of Pathology, Boston City Hospital, Boston.

1. (a) Russi, S.; Blumenthal, H. T., and Gray, S. H.: Small Adenomas of the Adrenal Cortex in Hypertension and Diabetes, *Arch. Int. Med.* **76**:284-291 (Nov.-Dec.) 1945. (b) Goldzieher, M. A.: *The Adrenal Glands in Health and Disease*, Philadelphia, F. A. Davis Company, 1944, pp. 97-103.

2. Rinehart, J. F.; Williams, O. O., and Cappeller, W. S.: Adenomatous Hyperplasia of the Adrenal Cortex Associated with Essential Hypertension, *Arch. Path.* **32**:169-177 (Aug.) 1941. Russi and others.<sup>1a</sup>

3. (a) Moore, R. A.: *A Textbook of Pathology*, Philadelphia, W. B. Saunders Company, 1944, pp. 1068-1069. (b) Kaufmann, E.: *Pathology for Students and Practitioners*, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, pp. 1287-1288. (c) Broster, L. R., and others: *The Adrenal Cortex and Intersexuality*, London, Chapman & Hall, Ltd., 1938, pp. 163-164. (d) Grollman, A.: *The Adrenals*, Baltimore, Williams & Wilkins Company, 1936. (e) Russi and others,<sup>1a</sup> (f) Goldzieher.<sup>1b</sup>

microscopic description of the adrenal glands was recorded. Single or multiple adenomas of the adrenal cortex were noted in 216 of the 7,437 (2.86 per cent). The age and sex distribution is shown in table 1. The incidence was equal among males and females and low in the first three decades of life. A trend toward an increasing incidence in later years is suggested by the data, but beyond the fifth decade the differences are not statistically significant when compared with the total number of autopsies performed (table 2).

A study was made of the available clinical and pathologic data on the 100 most recent consecutive cases in which adenomas of the adrenal cortex were found. Twenty-five of the patients had hyper-

TABLE 1.—*Incidence of Adrenal Adenomas in 7,437 Autopsies (4,519 on Males, 2,918 on Females)*

1. Total number of adenomas: 216 (130 in males, 86 in females)									
2. Percentage with adenomas: 2.86 (2.88 in males, 2.84 in females)									
3. Percentage with adenomas by age groups:									
Age range.....	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Total.....	0	0	0.5	1.9	2.4	2.8	4.9	3.5	6.8
Males.....	0	0	0.0	2.1	2.2	2.4	5.3	3.3	8.1
Females.....	0	0	0.9	1.6	2.7	3.5	4.3	3.8	5.4

TABLE 2.—*Age Distribution by Percentage in 7,437 Autopsies (4,519 on Males, 2,918 on Females) at the Mallory Institute of Pathology, Boston City Hospital*

Age range...	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100
Total.....	9.3	2.7	5.3	8.2	14.7	20.8	21.0	14.7	3.1	0.2
Males.....	8.7	2.4	4.1	7.3	15.4	22.4	21.3	15.6	2.7	0.1
Females.....	10.3	3.2	7.3	8.8	13.8	18.4	20.6	13.5	3.8	0.3

tensive cardiovascular disease, and 3 had diabetes mellitus. In 1,353 unselected consecutive autopsies performed in 1945 and 1946 the incidence of hypertensive cardiovascular disease was 14.6 per cent and that of diabetes mellitus was 3.4 per cent. Although the incidence of hypertensive cardiovascular disease is 10 per cent higher among the patients with adrenal adenomas, this is probably not significant because the 1,353 consecutive autopsies involved patients of all ages (one fourth under the age of 40) whereas the youngest patient with an adenoma of the adrenal cortex in the series of 100 studied was 42 years. Since hypertensive cardiovascular disease is most commonly encountered in patients past the age of 40, the incidence among the 100 cases probably reflects this variable. It is apparent that the incidence of diabetes mellitus was the same in the 100 cases in which there was adenoma of the adrenal cortex as in the 1,353 unselected autopsies.

In the series of 100 cases a weight above 350 Gm. was recorded for the heart in 51. Since such a weight, in the absence of valvular

disease, is considered in adults to be suggestive of hypertension,<sup>1a</sup> reports on 200 consecutive autopsies on patients above the age of 14 years, in which the heart had been weighed, were reviewed. In a total of 124 (62 per cent) the heart weighed over 350 Gm. These data fail to show an increased incidence of cardiac enlargement in patients with adenomas of the adrenal cortex.

There were 21 of the patients with adenomas of the adrenal cortex for whom microscopic pictures of the gonads were available for review. In 12 of these involutionary changes were found.<sup>4</sup> Inasmuch as changes of this nature are expected in approximately half of the patients in

TABLE 3.—*Incidence of Cardiac Involvement and Diabetes in Patients with Adrenal Adenomas as Compared with That in Unselected Autopsies*

A. Incidence of hypertensive cardiovascular disease and diabetes as diagnosed on combined clinical and pathologic evidence in 1,353 autopsies *			
	Hypertensive Cardiovascular Disease	Diabetes	
Total number .....	198	46	
Percentage .....	14.6	3.4	
B. Incidence of hypertensive cardiovascular disease, diabetes and increased weight of the heart (greater than 350 Gm.) in one hundred patients with adrenal adenomas †			
	Hypertensive Cardiovascular Disease	Diabetes	Heart Weight Above 350 Gm.
Total number .....	25	3	51
Percentage .....	25	3	51
C. Incidence of increased weight of the heart (greater than 350 Gm.) in two hundred autopsies on adults			
Total number, 124; percentage, 62			

\* These were unselected consecutive autopsies on a group which included patients in the first four decades of life.

† The age of the patients ranged from 42 to 89 years.

this age range, no relationship between gonadal changes and adenomas of the adrenal cortex is suggested.

#### COMMENT

The literature concerning adenomas of the adrenal cortex is difficult to interpret accurately because of differences in criteria in the classification of enlargement of the adrenal cortex. (For a review of adrenal hypertrophy see Tepperman, Engel and Long.<sup>5</sup>) Moore<sup>3a</sup> stated: "The frequency of local hyperplasia and adenoma of the adrenal cortex is in indirect ratio to the exactness of criteria and examination. Most adrenals contain some type of spherical mass. Grossly demonstrable

4. The criteria used were (1) the amount of fibrosis, (2) the follicular or spermatogenic activity, (3) the thickness of the lamina propria and the number of Leydig cells in the testes and (4) the appearance of corpora lutea in the ovaries.

5. Tepperman, J. F.; Engel, F. L., and Long, C. N. H.: A Review of Adrenal Cortical Hypertrophy, *Endocrinology* 32:373-402 (May) 1943.

nodules are present in about 10 per cent of all adults." Torgersen<sup>6</sup> suggested that medullary nodules are no more than an indication of the fact that the cortical-medullary margin is extremely irregular and folded and that the "islands" actually are "peninsulas" which seem isolated because of the angle in which the section has been cut. Goldzieher<sup>1b</sup> asserted that adenomatous nodules are observed in about 33 per cent of all adults regardless of age or sex. Grollman<sup>3d</sup> reported that cortical hyperplasia may occur either in the form of diffuse hyperplasia or as circumscribed nodules ranging in size from microscopic islets of tissue to the size of a hen's egg and that it is an incidental finding in about a third of all autopsies. Russi, Blumenthal and Gray<sup>1a</sup> reported the presence of small adenomas of the adrenal cortex in 1.45 per cent of 9,000 consecutive autopsies.

This study does not include so-called diffuse hyperplasia or "true" cortical adenomas (with complete capsule) as defined by Ewing.<sup>7</sup> The terms adenomatous hyperplasia, focal adenomas and cortical adenomas are used by various authors in their discussions of the pathologic findings described. A surgical study such as that of Castleman and Smithwick<sup>8</sup> is concerned only with adrenal tumors which are observable grossly. The observed incidence of 2.86 per cent confirms the belief that adenomas of the adrenal cortex are not unusual in adults of either sex. The age distribution suggests an increasing incidence with advancing years.

Russi, Blumenthal and Gray<sup>1a</sup> concluded that "hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general autopsy group." Rinehart, Williams and Cappeller<sup>2</sup> have stated: "The correlation of hyperplasia of the adrenal cortex with essential hypertension is almost as definite as that of hyperplasia of the thyroid gland with exophthalmic goiter." Dempsey,<sup>9</sup> reviewing autopsy material similar to that on which Rinehart and his colleagues based their conclusions, found no significant difference in the weight or structure of the adrenals of those with hypertension and of those without it. Moore<sup>3a</sup> has written that there is no established relation between focal hyperplasia and adenoma of the adrenal cortex and hypertension.

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6. Torgersen, O.: *Histological Studies on the Normal and the Irradiated Suprarenal Gland in Rabbits*, Oslo, I Kommisjen Los Jacob Dyburad, 1940.

7. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1941, pp. 830-831.

8. Castleman, B., and Smithwick, R. H.: *The Relation of Vascular Disease to the Hypertensive State Based on Study of Renal Biopsies from One Hundred Hypertensive Patients*, J. A. M. A. **121**:1256-1261 (April 17) 1943.

9. Dempsey, W. S.: *The Adrenal Cortex in Essential Hypertension*, Arch. Path. **34**:1031-1034 (Dec.) 1942.

Selye has presented evidence<sup>10</sup> of a relationship between adrenal function and hypertension. However, the data presented here fail to indicate that the morphologic abnormality under study is related to or indicative of pathologic changes producing hypertensive cardiovascular disease. The incidence of diabetes mellitus and cardiac enlargement was essentially the same in our series of patients with adenomas of the adrenal cortex as in the control groups.

Broster<sup>3c</sup> has suggested that the focal hyperplasias of the adrenals, prostate and breast are related to involutionary processes of the gonads. Woolley, Fekete and Little<sup>11</sup> reported that gonadectomy in a selected strain of mice led almost invariably to adrenal neoplasms. Adenomas of the adrenal cortex could possibly constitute an adrenal compensatory mechanism for waning or absent gonadal steroid output. If this premise were true, cellular or architectural changes in the gonads would be helpful evidence. However, no gonadal changes were found which were greater than those observed in routine autopsies on patients of a similar age group.

#### SUMMARY

Adenomas of the adrenal cortex larger than 3.0 mm. were encountered in 216 (2.86 per cent) of 7,437 consecutive autopsies in which the adrenals were observed. The incidence was the same in males as in females. An adenoma was found in only 4 patients under the age of 40 years. A progressively greater incidence with increasing age was noted.

There was no significant difference in the incidence of hypertensive cardiovascular disease, cardiac enlargement, diabetes mellitus or gonadal changes in patients with adenomas of the adrenal cortex as compared with that in patients without such tumors.

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10. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, *J. Clin. Endocrinol.* **6**:117-230 (Feb.) 1946.

11. Woolley, G. W.; Fekete, E., and Little, C. C.: Gonadectomy and Adrenal Neoplasms, *Science* **97**:291 (March 26) 1943.

# METABOLIC STUDIES IN DIABETIC ACIDOSIS

## II. The Effect of the Administration of Sodium Phosphate

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IT IS now well recognized that the phosphate cycle constitutes the mechanism whereby energy resulting from oxidation is rendered available to living cells.<sup>1</sup> A notable rise in the plasma level and urinary excretion of phosphorus has been found in diabetic acidosis.<sup>2</sup> This apparently causes a significant depletion of phosphorus stores in the body, as shown by the response to insulin. The plasma and urinary phosphorus levels fall precipitously and remain subnormal for as long as a week after institution of insulin therapy.<sup>2b</sup>

The fact that death may occur in circulatory collapse after abolition of ketosis, restoration of a normal blood sugar level and replacement of apparently adequate amounts of water and sodium chloride raises

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Read by title at the meeting of the American Society for Clinical Investigation, May 1946.

From the Department of Medicine of Wayne University College of Medicine and the City of Detroit Receiving Hospital.

1. Lipmann, F.: Metabolic Generation and Utilization of Phosphate Bond Energy, in Nord, F. F., and Werkman, C. H.: *Advances in Enzymology*, New York, Interscience Publishers, Inc., 1941, vol. 1, p. 91.

2. (a) Atchley, D. W.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: A Detailed Study of Electrolyte Balances Following the Withdrawal and Re-Establishment of Insulin Therapy, *J. Clin. Investigation* **12**:297, 1933. (b) Guest, O. M., and Rapoport, S.: Role of Acid Soluble Phosphorus Compounds in Red Blood Cells in Experimental Rickets, Renal Insufficiency, Pyloric Obstruction, Gastroenteritis, Ammonium Chloride Acidosis and Diabetic Acidosis, *Am. J. Dis. Child.* **58**:1072 (Nov.) 1939. (c) Harrop, G. A., and Benedict, E. M.: Participation of Inorganic Substances in Carbohydrate Metabolism, *J. Biol. Chem.* **59**:687, 1924. (d) Kaplan, N. O.; Franks, M., and Friedgood, C. E.: Metabolism in Diabetic Coma Produced by Alloxan, *Science* **102**:447, 1945.

the question of the clinical importance of deficiency of other elements, notably phosphorus and potassium. One of the objectives of the present study was to determine the clinical efficacy of intravenously administered sodium phosphate as an adjuvant to the therapy of diabetic acidosis.

The method of study and the clinical material were described in detail in a preceding paper. The results are presented in tables 1 to 12 inclusive of the preceding paper and in tables 1 and 2 of this communication. The patients receiving phosphorus also were treated with large amounts of dextrose. Therefore, for the most part the dextrose-treated patients serve as the controls.

### RESULTS

*Plasma Inorganic Phosphorus Levels on the Patients' Admission to the Hospital.*—The plasma inorganic phosphorus level was definitely elevated in 28 patients prior to treatment, ranging from 4.23 to 17.20 mg. per hundred cubic centimeters and averaging 7.88 mg. The level could not be correlated with the blood sugar content, the degree of acidosis, or the clinical state as measured by the blood pressure, mental state or complications.

*Effect of Insulin on Plasma and Urinary Phosphorus Levels.*—The plasma inorganic phosphorus level fell precipitously during the first four to five hours in all but 2 cases. By the end of the first period it was below 1 mg. per hundred cubic centimeters in 5 cases, between 1 and 2 mg. in 12 cases and between 2 and 3 mg. in 6 cases (table 1). In cases 11 and 12 the level did not change significantly during the first four hours of treatment despite apparent glucose retention and combustion but fell subsequently to below 1 mg. by the end of ten hours in the former and after twenty-four hours in the latter. The lowest level during the first day of treatment was less than 1 mg. per hundred cubic centimeters in 10 cases and between 1 and 2 mg. in the remaining 18.<sup>3</sup> From a comparison of the patients treated with dextrose during the first four hours and those not so treated, it is evident that the early administration did not accelerate the fall in plasma inorganic phosphorus or the rate of its urinary excretion. As a matter of fact, the decrement in plasma inorganic phosphorus during the first period was slightly greater and more precipitous in the group receiving only insulin and sodium chloride than in the group receiving supplementary dextrose. This may be attributable to the poorer clinical and metabolic state of the dextrose-treated patients.

The striking fall in the level of plasma inorganic phosphorus cannot be accounted for by excretion through the urine. This is illustrated

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3. These figures include some interval determinations not shown in the table.



TABLE 1.—*Phosphorus Metabolism.*

Group	Case	Plasma Phosphorus, Mg./100 Cc.					Urine Phosphorus, Mg. per Hr.				24 Hour Urinary Phosphorus		Urinary Phosphorus in Periods 2, 3 and 4	
		Admision	Period				1	2	3	4	Total Mg.	Mg. per Hr.	Total Mg.	Mg. per Hr.
			1	2	3	4								
Saline.....	1	7.56	2.77	1.05	2.84	0.90	21.3	5.1	5.2	6.7	200.9	8.1	115.7	6.8
	2	7.68	1.53	2.43	1.69	1.85	52.2	15.3	19.7	4.9	533.3	22.2	246.0	13.3
	3	10.12	1.21	0.83	0.26	2.53	104.0	7.6	1.9	4.6	511.4	21.3	95.4	4.8
	4	9.60	2.44	2.44	1.65	0.88	158.2	82.3	48.3	10.1	1,649.0	98.6	700.0	38.8
	5	8.80	1.08	1.38	1.69	2.75	40.1	2.8	5.8	4.8	276.1	11.5	95.6	4.9
	6	8.37	1.76	—	—	—	51.8	—	—	—	—	—	—	—
	7	10.03	1.65	1.00	1.29	1.98	64.6	15.6	17.6	—	591.0	21.7	206.0	11.4
Average.....		8.88	1.78	1.52	1.57	1.84	70.3	21.5	16.4	6.2	627.4	26.1	243.1	13.2
Dextrose.....	8	17.20	4.26	1.76	1.22	1.80	0	0	15.9	3.2	—	—	—	—
	9	4.28	1.60	0.16	0.80	0.44	11.3	6.9	4.3	3.7	150.7	6.3	85.8	4.7
	10	10.04	5.24	0.96	0.46	—	91.8	67.4	11.2	—	—	—	—	—
	11	4.23	3.34	0.99	1.43	1.40	34.5	13.7	3.8	3.8	271.3	11.3	133.3	6.7
	12	8.14	8.51	5.17	3.60	0.54	29.3	20.8	30.4	18.0	1,530.0	64.9	1,442.0	72.1
	13	5.75	0.83	0.43	0.40	—	91.1	1.4	0.2	—	—	—	—	—
	14	7.41	1.06	1.06	1.43	1.18	13.7	0	0	0	82.0	3.5	0	0
	15	11.60	2.23	0.95	1.88	2.20	—	—	—	—	—	—	—	—
	16	4.50	0.32	0.14	0.08	1.08	35.3	3.8	3.9	1.8	172.5	7.2	66.5	3.2
	17	5.70	0.49	0.66	0.66	—	164.1	99.0	—	—	—	—	—	—
	18	7.65	1.46	1.17	1.69	1.48	92.8	19.7	6.1	5.3	540.9	22.5	169.9	8.5
Average.....		7.86	2.67	1.17	1.19	1.30	56.4	41.6	7.6	9.4	163.7	19.3	316.2	19.0
Phosphorus.....	19*	5.98	2.34	4.77	....	Receiving 1,319 Mg.-of Phosphorus	59.6	36.4	9.6	9.8	104.9	16.9	216.9	10.4
	20*	6.30	1.14	5.27	....	(0.82)†	59.1	136.0	—	—	—	—	—	—
	21	8.26	1.01	3.70	0.69	(1.87)†	47.2	92.5	17.3	5.4	599.7	29.2	305.9	21.5
	22	5.12	2.51	5.36	2.48	(1.44)†	27.1	11.7	35.6	21.1	636.1	27.7	574.8	27.8
	23	10.10	4.60	9.64	2.60	(1.65)†	66.3	71.2	36.4	3.9	638.3	26.6	406.9	19.8
						Receiving 2,688 Mg. of Phosphorus								
	24	7.20	0.94	5.30	2.07	—	40.1	19.0	18.2	1.7	402.6	19.7	174.6	11.8
	25	9.49	0.80	5.85	3.92	3.76	30.3	58.3	42.0	21.8	877.1	30.3	630.1	40.0
	26	7.15	1.29	6.00	2.76	(2.21)†	45.0	87.1	36.8	—	—	—	—	—
	27	6.20	1.73	7.46	1.37	—	71.7	—	122.2	35.7	1,481.8	49.2	895.0	44.8
	28	6.03	2.88	10.50	2.85	(1.00)†	11.7	173.5	111.2	30.3	1,432.4	59.7	1,196.1	65.3
Average.....		7.18	1.93	6.39	2.34	2.34	48.8	80.2	47.7	16.8	775.4	33.2	548.8	30.0

\* Plasma phosphorus was not determined at the end of the third period.  
† Figures indicate the lowest values in the third period.

by the patient in case 8, who was in complete anuria for the first eight hours, during which the level fell from 17.2 to 1.76 mg. per hundred cubic centimeters. It was also borne out by quantitative determinations of urinary phosphorus in the remaining cases.

Although there is no close agreement in the literature as to normal values for phosphorus excretion in nondiabetic patients or in those with controlled diabetes, the range is probably from 12.5 to 64 mg. per hour, with a mean of approximately 50 mg.<sup>4</sup> Urinary phosphorus excretion is known to be high in patients with uncontrolled diabetes<sup>5</sup> and was presumably increased in our cases prior to treatment. Urinary output of phosphorus fell within the normal range during the first four hours in 19 of 27 cases. In cases in which no supplementary phosphate was administered, the urinary level was invariably normal or subnormal after the ninth hour of treatment and was extremely low after the sixteenth hour in all but 1. Phosphorus excretion remained subnormal for as long as five days in such cases.

*The Fate of Injected Phosphate.*—Since previous studies and the foregoing data suggested that a deficiency of readily available phosphorus might exist in diabetic coma, buffered sodium phosphate solution<sup>6</sup> was given intravenously in 10 cases at a time when the plasma inorganic phosphorus was known to be low. The first 5 patients received 500 cc. of sodium phosphate solution containing 1,319 mg. of phosphorus. The injection was begun on an average of 3.95 hours after the patient came under treatment and was completed in an average period of 1.18 hours. The mean plasma inorganic phosphorus level at the end of the injection, 5.75 mg. per hundred cubic centimeters, was 3.42 mg. higher than the mean preinjection level of 2.33 mg. per hundred cubic centimeters. During the next few hours, a rather prompt return to normal or subnormal values took place. The rise in plasma inorganic phosphorus was relatively small in comparison with the fivefold to sixfold increase after similar doses in normal

4. Blatherwick, N. R.; Bell, M., and Hill, E.: Some Effects of Insulin on the Carbohydrate and Phosphorus Metabolism of Normal Individuals, *J. Biol. Chem.* **61**:241, 1924. Fiske, C. H.: Inorganic Phosphorus and Acid Excretion in the Post-Absorptive Period, *ibid.* **49**:171, 1921. Reiser, R.: Phosphorus Changes During the Absorption of Oil and Glucose, *ibid.* **135**:303, 1940. Robertson, J. D.: Calcium and Phosphorus Excretion in Thyrotoxicosis and Myxoedema, *Lancet* **1**:672, 1942. Sherman, H. C.: Phosphorus Requirements in Man, *J. Biol. Chem.* **40**:173, 1920. Walker, B. S.: Normal Relationships of Blood and Urine Phosphorus, *J. Lab. & Clin. Med.* **17**:347, 1931. Harrop and Benedict.<sup>2c</sup>

5. Atchley and others.<sup>2a</sup> Guest and Rapoport.<sup>2b</sup> Harrop and Benedict.<sup>2c</sup>

6. This was prepared according to the method of Ollayos and Winkler,<sup>7</sup> i. e., 12.33 Gm. of  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  and 1.12 Gm. of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  were dissolved in distilled water and the solution sterilized by boiling for thirty minutes. It was then made to volume (500 cc.) and the  $\text{pH}$  checked.

persons.<sup>7</sup> The urinary phosphorous level increased during the course of the injection but became normal shortly afterward and remained so for the rest of the twenty-four hours.

The total phosphorus excretion for the second, third and fourth periods in these first 5 patients averaged 376 mg. and was only 59.8 mg. greater than the average phosphorus output of the dextrose group. Since this output of 59.8 mg. in excess of that of the controls represents only 5 per cent of the 1,319 mg. administered, it would appear that 95 per cent of the injected phosphorus was retained.

Since the retention of almost 1,319 mg. of phosphorus failed to prevent subsequent hypophosphatemia, a larger dose was thought to be indicated. The second 5 patients were therefore given 2,638 mg. of phosphorus in 1,000 cc. of solution by slow intravenous injection

TABLE 2.—Average Retention of Administered Phosphorus (P) from the Beginning of Injection to the End of the First Twenty-Four Hours (Periods 2, 3 and 4)

Cases	(A) Admin- istered P, Mg.	(B) P Excreted by Phosphate- Treated Patients	(C) P Excreted by Controls	(D=B-C) Excretion of Admin- istered P,* Mg.	(E=A-D) Retention of Admin- istered P †	(F=E÷A) Per Cent Reten- tion ‡
5 cases in which 1,319 mg. of P was received	1,319	376	316	60	1,259	95
5 cases in which 2,638 mg. of P was received	2,638	722	316	406	2,232	85
Average of 10 cases	1,979	548	316	232	1,747	88

\* Excretion of administered P = P excreted by phosphate-treated patients minus P excreted by controls.

† Retention of administered P = administered P minus excretion of administered P.

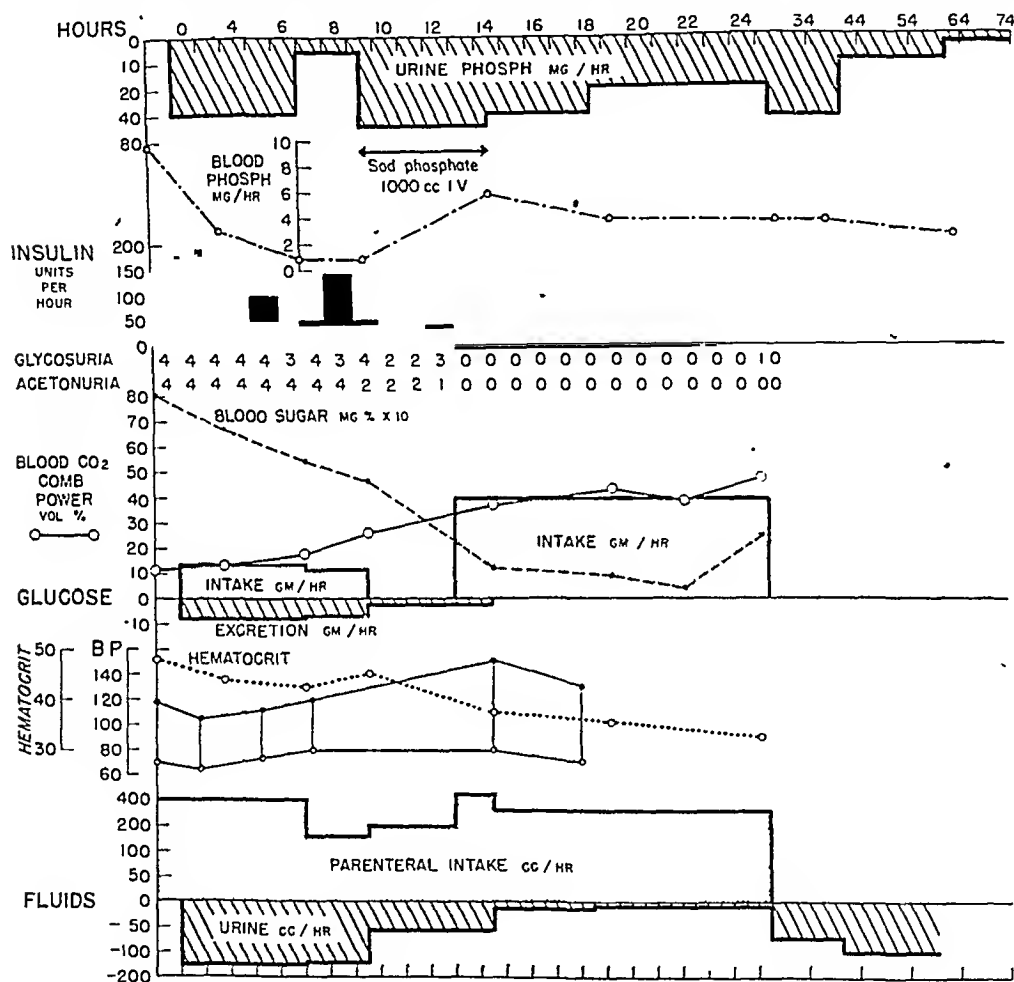
‡ Per cent retention = retention of administered P ÷ administered P.

over an average period of three and three-quarters hours. Doubling the dosage caused a greater rise in plasma inorganic phosphorus (5.49 mg. per hundred cubic centimeters as compared with 3.42 mg.) and a larger urinary output (721.6 mg. total for periods 2, 3 and 4 as compared with 376.0 mg.). Nevertheless, the plasma inorganic phosphorus subsequently fell to subnormal levels in 4 of these 5 patients, and hourly urinary excretion dropped below 50 mg. by the fourth period in all 5 receiving the larger dose. Furthermore, the apparent phosphorus retention at the end of twenty-four hours (calculated as before, with the dextrose group serving as controls) averaged 2,232.6 mg., or 85 per cent of the injected phosphorus. Thus the phosphate deficit in diabetic coma may not be corrected by administration of as much as 2,638 mg. of phosphorus.

7. Ollayos, R., and Winkler, A. W.: Urinary Excretion and Serum Concentration of Phosphate in Man, *J. Clin. Investigation* 22:147, 1943.

The effect of the injection of 1,000 cc. of sodium phosphate on blood and urinary phosphorus, carbohydrate metabolism and acidosis is illustrated graphically in the accompanying figure, which depicts the course in case 25.

Phosphorus retention was demonstrable for several days after recovery from diabetic coma. When urinary loss in the phosphate group is corrected with that in the dextrose control group, the apparent retention of the injected phosphorus averaged 88 per cent in 8 cases at the end of twenty-four hours and 57 per cent in 5 cases at the end



Results of injection of sodium phosphate in case 25.

of forty hours. Four of the phosphate group were followed for longer periods, and data were obtained on the time required for the total urinary output of phosphorus, as measured from the start of the intravenous injection, to exceed the amount administered in this injection. More than seventy-two hours were required in 3 cases, more than ninety-six hours in 2 and more than one hundred and twenty hours in 1. Since the patients received considerable supplementary phosphorus through regular diabetic diets instituted after the first twenty-four to forty-eight hours, it is evident that phosphorus excretion was

subnormal for several days and that phosphorus was being stored in the tissues.

*Effect of Sodium Phosphate on Carbohydrate Metabolism.*—At the end of the second period, the average blood sugar content in the patients who had just received sodium phosphate was 351 mg. per hundred cubic centimeters and was thus closely comparable to the average level of 367 mg. in the dextrose control group. Thereafter the blood sugar level fell more rapidly in the phosphate group than in the dextrose group, as shown by average levels of 285 mg. in the former and 334 mg. in the latter at the end of the third period and average values of 129 and 273 mg. respectively at the end of the fourth period (table 4 in the previous paper). The superior control of carbohydrate metabolism in the phosphate group during the third and fourth periods cannot be explained by differences in insulin and dextrose intake during these periods, since the differential was in favor of the dextrose controls. Thus the average intake of dextrose during the third and fourth periods was 5 Gm. per hour more in the phosphate group (table 5 in the previous paper) and the average insulin dose 6.5 units per hour less in the phosphate group than in the dextrose control group (table 4 in the previous paper). These figures suggest that the partial correction of the phosphorus deficit accomplished through the administration of sodium phosphate had a favorable effect on carbohydrate metabolism. However, the data do not justify a positive conclusion because of the relatively small number of cases and because of a possible advantage which the phosphate group might have derived through the larger doses of insulin in the first period and the lower intake of dextrose during the first two periods.

*Effect of Sodium Phosphate on Acidosis.*—The degree of acidosis on admission of the patients to the hospital was greatest in the phosphate group and least in the saline group, as indicated by the clinical gradation of depression of consciousness, which averaged 3.1 for the phosphate group, 2.5 for the dextrose group and 2.0 for the saline group (table 1 in the previous paper), and by the carbon dioxide-combining power, which averaged 11.7, 14.0 and 16.1 volumes per cent respectively for the three groups (table 4 in the previous paper). Nevertheless the average time required for the disappearance of acetone from the urine was almost the same for the three groups. Return of consciousness was much more rapid during the administration of sodium phosphate than during a parallel period in the dextrose and saline controls. This will be elaborated on in the discussion of the clinical effects of sodium phosphate.

In order to ascertain the immediate effects of the administration of sodium phosphate on the carbon dioxide-combining power, all patients for whom the latter had been determined just before and

directly after the injection of the sodium phosphate were compared with the saline and dextrose controls, for whom the carbon dioxide-combining power had been obtained at the end of both the first and the second periods.<sup>8</sup> Among the 8 phosphate cases the carbon dioxide-combining power averaged 20 volumes per cent just before the start of injection of sodium phosphate and 30.2 volumes per cent after completion of the injection 2.75 hours later. Among the 14 control cases the carbon dioxide-combining power averaged 22.6 volumes per cent at the end of period 1 and 27 volumes per cent at the end of period 2, 4.04 hours later. Thus the average rise in the carbon dioxide-combining power during administration of sodium phosphate was 3.71 volumes per cent per hour, whereas the rise in the control cases during a comparable period was 1.09 volumes. The more rapid rise in the phosphate group may be due in part to a greater intake of sodium, since the total intake averaged 1.48 Gm. per hour in the phosphate cases during period 2 and 1.15 Gm. per hour in the controls during the same period. The difference in total hourly intake of sodium will not fully account for the greater rise of carbon dioxide-combining power and suggests that the sodium in the form of phosphate is better utilized for combating acidosis than the sodium ion in the form of sodium chloride, which was given to the controls. This might be anticipated from the fact that chloride remains almost entirely in the extracellular space in combination with sodium<sup>9</sup> whereas phosphate ion rapidly enters the cell,<sup>10</sup> leaving sodium behind to increase the alkaline reserve.

*Effects of Phosphate on Water and Chloride Balance.*—The data are difficult to interpret because of the variability in the cardiovascular status and the lack of information on blood volume, extracellular space and sodium and potassium output. Nevertheless, certain observations are noteworthy. Retention of water during the second, third and fourth periods—expressed in terms of either the total volume or the percentage of intake retained—was greatest in the phosphate group and least in the dextrose group. The phosphate group retained a total of 4,826 cc., or 71 per cent of the intake, during these periods, the saline group a total of 3,694 cc., or 69 per cent of the intake, and the dextrose

8. The data on cases 3, 6, 18 and 23 were eliminated because determinations of carbon dioxide-combining power were not available at both the beginning and the end of the period. The data on case 2 were also eliminated because the carbon dioxide-combining power had been raised at the beginning of the period to 63 volumes per cent by an infusion of sodium bicarbonate.

9. Peters, J. P.: *Body Water*, Springfield, Ill., Charles C Thomas, Publisher, 1935, p. 132.

10. Hevesy, G.: *Application of Radioactive Indicators in Biology*, in Luck, J. M.: *Annual Review of Biochemistry*, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 9, p. 641.

group a total of 3,498 cc., or 50 per cent of the intake. In the interpretation of these figures, it is necessary to take into consideration the sodium intake, which favors water retention, and the glucose output, which promotes diuresis. The average intake of sodium ion for the second, third and fourth periods was 8.30 Gm. in the phosphate group, 6.43 Gm. in the saline group and 11.75 Gm. in the dextrose group. Total glucose outputs during the same interval were 70.9 Gm., 38.4 Gm. and 159.3 Gm. for the three groups respectively. In a comparison of the phosphate and dextrose groups, it is seen that the higher intake of sodium ion favored water retention in the latter, whereas the greater glucose output predisposed to diuresis. Similarly, the higher sodium intake in the phosphate group than in the saline group favored water retention in the former, while the greater glycosuria had the opposite effect.

The average value for the hematocrit reading on admission to the hospital was almost the same in the three groups, amounting to 54.1 per cent in the phosphate group and 54.7 per cent in both the saline and the dextrose controls (table 8 in the previous paper). The level at the end of the first period was likewise comparable, as shown by the figures of 42.6, 42.9 and 45.6 per cent for the three groups respectively. Thereafter the values for the hematocrit reading differed in the phosphate and control groups. Successive readings over a twenty hour period following the beginning of sodium phosphate injection revealed a progressive hemodilution, as shown by a drop from 42.6 to 36.6 per cent. Meanwhile the value was maintained at a plateau in the saline controls and was more irregular in the dextrose group, with a slight drop in the last specimen. The greater and more prolonged hemodilution in the phosphate group than in the control group suggests that phosphate administration may have aided in the retention of water in the vascular tree.

The plasma chloride was maintained at a higher and more constant level during the second, third and fourth periods in the phosphate group than in the saline or dextrose controls in spite of a lower chloride intake in the former during these periods (table 9 in the previous paper). This may be due to the release of chloride from the red cells as a result of more rapid restoration of organic phosphates in the cells when phosphate is given.

*Clinical Effect of Administration of Sodium Phosphate.*—No toxic manifestations were observed with either the 500 cc. or the 1,000 cc. dose of sodium phosphate solution. There was no evidence of latent or manifest tetany in any case. The serum calcium content was determined in a few cases, and no significant depression was revealed.

In the investigation of 71 successive cases of diabetic coma (table 12 in the previous paper), we found only one fatality among patients with

a severity index<sup>11</sup> below 30 per cent and no recovery among those with a severity index over 60 per cent. The outcome in the patients with a 30 to 60 per cent range was influenced by the therapeutic regimen. The poorest results were obtained in patients to whom dextrose was administered early. Of 18 such patients with an average severity index of 44 per cent, 12 (or 67 per cent) died. Among 11 patients who received dextrose early and sodium phosphate subsequently the severity index was 44 per cent and the actual death rate 27 per cent. Among 7 patients for whom administration of dextrose was postponed until the blood sugar level reached normal the severity index was 38 per cent and the fatality rate 42 per cent. Thus the administration of sodium phosphate seems to have modified the deleterious effect of early dextrose administration. Whether the use of sodium phosphate in cases in which dextrose is withheld until the blood sugar level falls to normal would further reduce the fatality rate remains to be determined in later work.

The most striking clinical effect was the improvement in mental state which seemed to coincide with the administration of sodium phosphate. The 3 patients who were unconscious at the start of the injection regained consciousness during its course. On the other hand, only 1 of the 5 controls regained consciousness during a comparable period. The improvement in mental state is further reflected in the greater over-all rise in the level of consciousness during the second period in the phosphate group than in the saline or dextrose controls. We have since observed this phenomenon of return of consciousness with administration of phosphate in patients who subsequently lapsed into coma and died.

A rise in systolic blood pressure was a fairly constant phenomenon, occurring in 9 of 10 cases, but the diastolic pressure varied only slightly. It was hoped that sodium phosphate might have a specific effect in shock associated with diabetic coma. However, in case 19 administration of 500 cc. of sodium phosphate failed to check a falling blood pressure. Because of approaching shock levels at the end of phosphate injection, 500 cc. of plasma was given, after which there was a distinct rise of blood pressure and shock was averted.

#### COMMENT

Since insulin is intimately concerned with the phosphorylation of glucose,<sup>12</sup> which is the necessary initial step for oxidation or storage

11. Collen, M. F.: Mortality in Diabetic Coma, *Arch. Int. Med.* **70**:347 (Sept.) 1942.

12. Price, W. H.; Cori, C. F., and Colowick, S. P.: The Effect of Anterior Pituitary Extract and of Insulin on the Hexokinase Reaction, *J. Biol. Chem.* **160**: 633, 1945.



as glycogen, lack of insulin should lead to an accumulation of inorganic phosphate and unphosphorylated glucose. An elevation of plasma and urinary inorganic phosphorus levels in diabetic acidosis and a precipitous fall after insulin therapy have been demonstrated by others<sup>13</sup> and confirmed by our data. The probable mechanism of these changes was brought out by the findings of Guest and Rapoport<sup>2b</sup> and Kaplan, Franks and Friedgood.<sup>2d</sup> The former showed that the organic acid-soluble phosphorus compounds of the red blood cells fell markedly in diabetic acidosis and rose in response to insulin therapy. Using rats with diabetes induced by alloxan, the latter demonstrated that the development of coma was accompanied with a decrease in the organic phosphates of the liver (chiefly adenosine triphosphate and adenosine diphosphate) and an increase in the inorganic phosphate of the liver and plasma. Under insulin therapy the inorganic phosphate levels in the plasma and liver fell, while the organic phosphates of the liver increased. Thus, the elevation of the inorganic phosphate level in the plasma and urine during diabetic acidosis may be due to the breakdown (or failure of reconstitution) of organic phosphates because of the depressed oxidation resulting from lack of insulin. The fall in plasma and urinary inorganic phosphate levels during insulin therapy is probably due to the resumption of phosphorylation, with subsequent reconstitution of the organic phosphate compounds of the body.

During the development of diabetic acidosis, Atchley and others<sup>2a</sup> demonstrated an increase in urinary output of phosphorus sufficient to cause a significant depletion of this element. The presence of a considerable phosphorus deficit in diabetic acidosis was indicated by the data of Guest and Rapoport<sup>2b</sup> and by the observations reported in this communication. The patients who received sodium phosphate solution exhibited a great avidity for the phosphorus, which was apparently deposited rapidly in the tissues. The maximum rise in plasma inorganic phosphorus obtained with 2,638 mg. was 7.72 mg. per hundred cubic centimeters, as compared to the 10.10 to 17.86 mg. rise obtained in normal persons given the same quantity.<sup>7</sup> In the normal persons 55 to 68 per cent of the administered phosphorus was excreted in six to twelve hours. In our cases an average of only 28 per cent was recovered from the urine over a period of eighteen hours. Other avenues of excretion were not investigated but probably played only a minor role, since Hevesy,<sup>10</sup> using radioactive phosphorus as a tracer,

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13. Kay, H. D., and Robison, R.: Effect of Insulin Administration on the Distribution of the Phosphorus Compounds of Blood and Muscle, *Biochem. J.* **18**: 1139, 1924. Perlzweig, W. A.; Latham, E. and Keefer, C. S.: Behavior of Inorganic Phosphate in the Blood and Urine of Normal and Diabetic Subjects During Carbohydrate Metabolism, *Proc. Soc. Exper. Biol. & Med.* **21**:33, 1923. Guest and Rapoport.<sup>2b</sup> Harrop and Benedict.<sup>2c</sup> Kaplan and others.<sup>2d</sup>

calculated that only one eighth of the phosphorus absorbed into the body was excreted by routes other than the urinary tract. Despite the administration of this supplemental phosphorus, subnormal urinary excretion persisted in all our cases throughout the period of study (six days in 1 case). From two to five days were required for the total urinary phosphorus output to equal the amount given intravenously, even though liberal amounts were included in the diet after the first day. Thus the significant phosphorus deficit associated with diabetic acidosis was only partially replenished by the amounts of phosphorus given to our patients.

In view of the importance of phosphorylated compounds in carbohydrate metabolism, a distinct improvement in carbohydrate utilization might be anticipated in the phosphate-treated patients. Indeed, Friedlander and Rosenthal<sup>14</sup> observed a fall in the blood sugar content in diabetic patients given infusions of sodium phosphate without insulin. We have confirmed this in a single unreported case. In this series of cases of diabetic acidosis the blood sugar was better controlled and carbohydrate appeared to be utilized more efficiently when phosphate was administered than when it was withheld. Since the total number is small and since individual cases in the phosphate and dextrose control groups differed considerably in initial severity and in dextrose and insulin dosage, the series must be extended before positive conclusions can be drawn in regard to the effect of exogenous phosphate on carbohydrate metabolism.

No acceleration in the rate of disappearance of acetonuria was demonstrable after the administration of sodium phosphate. The greater rise in carbon dioxide-combining power and the superior maintenance of plasma chloride levels are expected from the transfer of phosphate ion to the cells. This transfer leaves the sodium ion free to increase the alkaline reserve. Chloride and organic phosphate concentrations are in a reciprocal equilibrium, at least in the red blood cells.<sup>15</sup> Thus, when the organic phosphate level rises in the red cell, chloride shifts from cell to plasma. This presumably accounts, at least in part, for the maintenance of high serum chloride levels in the phosphate group despite the relatively low chloride intake. The greater hemodilution suggests that sodium phosphate may promote retention of water in the vascular bed. The mechanism remains obscure.

The most striking clinical effect was the rapid improvement in mental state which accompanied the administration of sodium phos-

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14. Friedlander, I., and Rosenthal, W. G.: Ueber den Einfluss des Phosphorsäueresions auf dem Blut und Harnzucker des normalen und des diabetischen Organismus, *Arch. f. exper. Path. u. Pharmakol.* **112**:65, 1926.

15. Guest, G. M., and Rapoport, S.: Organic Acid Soluble Phosphorus Compounds of the Blood, *Physiol. Rev.* **21**:41, 1941; footnote 2b.

phate. This may be traceable to the fact that carbohydrate is the preferred if not the sole fuel for the brain.<sup>16</sup> When an increased supply of phosphate is made available to the central nervous system; an increased efficiency of phosphorylations and hence of carbohydrate utilization may result. The presumed metabolic improvement might be reflected in the clearing of consciousness.

A second important clinical effect of administration of phosphate is the apparent improvement in fatality rate. Although the number of cases is small, application of the "chi squared" test for statistical significance to the dextrose and phosphate groups with 30 to 60 per cent severity indexes gives a P (probability) value of 0.07, indicating that only a small chance exists that the lowering in fatality rate is independent of the administration of phosphate. Comparison of the phosphate group with the saline group in which the condition was of equal or lesser severity again shows an apparent improvement in fatality rate, but the difference is not statistically significant and could have been due to chance.

It is difficult to attribute the improved survival rate to any single one of the effects of phosphate administration described here. The replenishment of the lost phosphate probably brought about a more rapid restoration of the depleted phosphorylated compounds of the cells. As has been pointed out, these organic phosphates are important because of their role in intermediary metabolism and because they are the reservoirs of energy derived from metabolic processes.<sup>1</sup> Thus, any measure, such as administration of inorganic phosphorus, which may help the resynthesis of these energy-rich organic phosphates may aid in restoration of normal cellular function. The potential importance of restoration of organic phosphates is indicated by the work of LePage<sup>17</sup> on tissue analyses in rats subjected to traumatic shock. The animals that succumbed to shock had severe depletion of the energy-rich organic phosphates in the most vital organs, including the brain. The animals that survived the trauma showed the ability to readjust their organic phosphates rapidly after the shocking procedure.

Patients with diabetic coma may die in shock even after the abolition of ketosis, the establishment of normal blood sugar levels and the administration of apparently sufficient amounts of plasma, sodium chloride and water. The administration of sodium phosphate may fail to restore a falling blood pressure and may not prevent shock. This necessitates consideration of the possible etiologic role of other deficiencies, especially the potassium deficit which accompanies the devel-

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16. Himwich, H. E., and Nahum, L. H.: The Respiratory Quotient of the Brain, *Proc. Soc. Exper. Biol. & Med.* **26**:496, 1929.

17. LePage, G. A.: Biological Energy Transformation During Shock, as Shown by Tissue Analyses, *Am. J. Physiol.* **146**:267, 1946.

opment of diabetic acidosis.<sup>2a</sup> Holler<sup>18</sup> recently reported a case in which the patient exhibited progressive muscular weakness and respiratory distress between the twelfth and twenty-first hour of treatment, at which time the serum potassium was found to be 2.5 milliequivalents. Prompt recovery followed the administration of potassium chloride. It is known that potassium, as well as phosphorus, follows dextrose into and out of the cells. It seems logical that potassium phosphate solutions might be of greater value than the sodium phosphate used in this study.

#### SUMMARY

The effect of the administration of buffered sodium phosphate solution, containing 1,319 to 2,638 mg. of phosphorus, has been studied in 16 cases of severe diabetic acidosis. Phosphorus, glucose, water and chloride balances are presented for 10 of these cases. The results are compared with those in control subjects who were treated with early administration of dextrose and in subjects not so treated, both groups receiving no sodium phosphate.

The plasma inorganic phosphorus level was elevated in all cases prior to treatment. A precipitous fall in the plasma level and in the urinary excretion occurred when insulin was given. The protracted subnormal phosphate excretion during convalescence reflected a profound depletion of phosphorus stores prior to treatment. A marked retention of injected phosphorus was demonstrated in all cases. Nevertheless, the dosage used was insufficient to correct completely the deficit, as shown by the subsequent drop in urinary inorganic phosphorus to subnormal levels.

The administration of sodium phosphate was accompanied with (a) a tendency toward improved utilization of carbohydrate, (b) a rise in plasma chloride and in carbon dioxide-combining power, (c) an apparent retention of fluid in the vascular system, (d) a rapid clearing of the mental state and (e) a statistically significant decrease in fatality rate.

The results of this study suggest that the therapeutic regimen in diabetic coma should include the parenteral administration of sodium phosphate four to eight hours after the first dose of insulin.

The results are discussed in the light of current opinion on the role of phosphate in carbohydrate metabolism.

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18. Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, *J. A. M. A.* **131**:1186 (Aug. 10) 1946.

# CHRONIC RECURRENT PANCREATITIS

A Clinical Study of Twenty Cases

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CHRONIC pancreatitis is an entity characterized by recurrent episodes of pain in the upper part of the abdomen. The diagnosis is seldom considered clinically, presumably because of limited familiarity with the various manifestations of the disease. The purpose of this paper is to review the significant manifestations as observed in

TABLE 1.—*Chronic Pancreatitis in Twenty Patients*

	Number
Sex	
Male.....	12
Female.....	8
Age, Yr.	
20 to 29.....	1
30 to 39.....	6
40 to 49.....	3
50 to 59.....	6
60 to 69.....	2
70 to 79.....	2

20 patients and to direct attention to certain features which may be helpful in the diagnosis.

## SEX AND AGE

The series comprises 12 men and 8 women. Reference to table 1 indicates that persons under 50 years of age were affected as often as those over 50. The predominance of males is in accord with other observations. Friedenwald<sup>1</sup> noted 14 males in a group of 25 patients and Vachon<sup>2</sup> 5 in a group of 6 patients, and Comfort and others<sup>3</sup>

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1. Friedenwald, J.: Acute and Chronic Pancreatitis, South. M. J. **30**:1067-1074, 1937.

2. Vachon, M. A.: Painful Forms of Chronic Pancreatitis, Lyon méd. **167**: 337-340, 1942.

encountered 25 in a series of 29. The age incidence, as given in the three reports, varied. While chronic pancreatitis was found in persons of all ages, its incidence appeared to be greater among those under 50.

#### DURATION OF SYMPTOMS

The duration of symptoms varied widely. In 8 patients the distress had been present for less than a year at the time of initial observation, while in 10 symptoms had been noted intermittently for three to five years. One man experienced repeated attacks of abdominal pain for ten years and another for thirty years. The intervals between acute attacks of pain ranged from two days to six months. Mild transitory abdominal discomfort and vague digestive disturbances, however, were present almost constantly in the majority of patients.

#### SYMPTOMS

Pain was the most frequent and outstanding complaint (table 2), occurring in 17 of the 20 patients (85 per cent). In 16 it was described

TABLE 2.—*Symptoms of Chronic Pancreatitis*

Symptoms	Percentage
Dyspeptic symptoms.....	100
Severe postprandial distress.....	85
Postprandial emesis.....	65
Loss of weight.....	60
Bouts of jaundice.....	40
Chills, sweats and fever.....	35

as severe, constant and knifelike; in 1 it was diffuse and indefinite. In 10 it was localized in the epigastrium, and in 6 others it was present in the right upper part of the abdomen. Pain in the back was the outstanding symptom in 1 instance. Radiation of pain was noted by 6 of the 17 patients. In 3 it was referred to the lumbar area from the level of the twelfth thoracic vertebra to the level of the second lumbar vertebra, and in 3 others it was transmitted to the right scapular and interscapular areas. The distribution of referred pain did not follow any distinct pattern. The left side of the hypochondrium, a frequent site of transmitted pain from the pancreas, was not mentioned as a point of transmission by any of this group. Pain in the back, commonly noted in pancreatic carcinoma, occurred in only 3 cases. In this series the acute episodes of pain averaged three to six hours in duration and occasionally persisted for from twenty-four to seventy-two hours. In only 2 patients was the acute attack of pain transitory, and in these it lasted less than thirty minutes. Frequently in persons with prolonged distress the recurrent pain steadily increased in severity and

eventually necessitated hospitalization. The diagnosis for 3 patients without abdominal pain was established by the roentgenologic demonstration of pancreatic calcifications. Steatorrhea was present in all 3 and diabetes in 2. It should be noted, however, that severe pain may occur in the presence of pancreatic calcification. Calculi were found in the pancreatic ducts at operation in 2 of the 17 patients with attacks of pain.

Dyspeptic symptoms such as bloating, eructation and vague abdominal distress were described by the entire group. In 16 postprandial discomfort was considerable, and in 13 the ingestion of moderate quantities of food precipitated acute attacks of pain. Partial relief from pain was obtained by emesis in 10. Small frequent feedings tended to prevent the postprandial distress; alkalis had little or no effect.

Alcohol has been regarded as one of the precipitating factors in pancreatitis by some investigators. Clark,<sup>4</sup> in a study of the post-mortem findings in patients with chronic alcoholism, found 36 in whom pancreatitis was a contributing cause of death. In 19 it was acute, in 5 acute and chronic and in 9 chronic. In 3 fat necrosis was present. The ingestion of alcohol in large quantities was followed by severe and protracted bouts of pain in 2 of the present series. A history of the excessive ingestion of alcohol was not elicited for the remaining 18. In this series, therefore, alcohol seemed of little importance in the development of the disease.

Loss of weight occurred in 12 patients (60 per cent). In 8 without steatorrhea the losses varied up to 20 pounds (9 Kg.). In 4 with pancreatic insufficiency the loss of weight averaged more than 25 pounds (11 Kg.).

A history of recurrent jaundice with attacks of pain was obtained in 8 cases. It was moderate in 5 and severe in 3. Chills followed by fever and sweats preceded the icterus in 4. In 5 of the 8 patients obstruction of the common duct was observed at operation, but in no instance was there a stone present in the common duct. The operative findings are discussed in more detail later.

#### PHYSICAL EXAMINATION

The physical findings were varied, and no pathognomonic manifestations of pancreatitis could be discovered. Varying degrees of tenderness were noted during acute attacks of distress in the 17 patients with pain. In 5 of these with severe pain rigidity of the upper part of the abdomen was present. Three others with diffuse pancreatic calcification had no abdominal tenderness.

The liver was palpable in 3 patients at an average of 3 cm. below the right costal margin. Moderate jaundice was present in 2 of these.

4. Clark, E.: Pancreatitis in Acute and Chronic Alcoholism, *Am. J. Digest. Dis.* 9:428-431, 1942.

While the incidence of a palpable mass in carcinoma of the pancreas is approximately 30 per cent, abdominal masses are infrequent in pancreatitis. In 1 patient a moderately firm irregular tumor, approximately 5 cm. in diameter, which descended on respiration was noted in the right side of the hypochondrium. Preoperatively this was interpreted as a pancreatic neoplasm. Exploration disclosed an inflammatory mass in the uncinate process of the pancreas, with involvement of the surrounding structures.

In another case a mass the size of a grapefruit was present in the epigastrium. The preoperative diagnosis of a pancreatic cyst was confirmed at operation.

Variations in temperature were not of sufficient regularity during the acute episodes to be of diagnostic significance. In 8 patients the temperature ranged from 100.5 to 103.2 F. during episodes of pain. There was no correlation between the degree of fever and the severity of the disease.

#### LABORATORY DATA

The serum amylase content was measured in 8 patients (table 3). Increase of the level to 1,500, 1,261 and 500 units respectively was noted in 3 cases. In 4 the levels were within normal limits (135, 125, 100 and 90 units), and in 1 a lowered value (40) was obtained.

*Increase of the Serum Amylase Content.*—The following 3 cases illustrate examples of increased serum amylase content.

CASE 11.—A 44 year old housewife had been subjected to a cholecystectomy one year previously. She was admitted to the hospital with severe abdominal pain. The temperature was 100.5 F.; the leukocyte count was 16,000. Four days after her admission pain was still present. The serum amylase content at that time was 1,500 units; the value on the fifth day was 45 units and on the eighth day 176 units. At operation (on the ninth day of hospitalization) the pancreas was found to be markedly thickened and fibrotic. There was no evidence of pancreatic necrosis or hemorrhage, and "fat necrosis" was absent.

CASE 3.—A 33 year old minister with recurrent severe epigastric pain had had an increased serum amylase level demonstrated elsewhere during a previous acute attack. The abdomen was tender but not rigid. The temperature was 99 F. and the leukocyte count 21,000. The serum amylase level on the day of his admission to the hospital was 1,261 units, and on the following day it was 1,240 units. The acute attack subsided within forty-eight hours.

CASE 1.—A 44 year old white woman had had recurrent attacks of distress in the upper abdominal area for three years. Physical examination revealed moderate abdominal tenderness and a mass the size of a grapefruit in the epigastrium. There was no fever or leukocytosis. The serum amylase level, determined eighteen days after her admission to the hospital, was 1,261 units. Operation several days later revealed a cyst together with induration of the pancreas; there was no gross evidence of acute pancreatitis.

The mechanism of the variations in amylase is not clear. The operative findings suggest, however, that they are determined by the changes



TABLE 3.—Serum Amylase Content and Leukocyte *V* values with Clinical and Operative Data in Eight Cases

Case	Diagnosis	Type of Pain	Temperature, F.	Condition of Abdomen	Diabetic State	Steator- rhea	Operative Findings *	Leukocyte Count †	Serum Amylase Content
11	Chronic pancreatitis	Prolonged and severe	100.5	Marked rigidity	No	No	Induration of the pancreas	16,000	1,300
3	Recurrent pancreatitis	Three severe attacks	99.0	Moderate tenderness	No	No	.....	21,000	1,261
1	Pancreatic cyst	Moderate	98.6	Epigastric mass (grapefruit sized)	No	No	Cyst of body of pan- creas; diffuse indur- ation	8,000	500
9	Obstruction of the common duct secondary to pancreatic cyst	Severe	98.6	Normal	No	No	Cyst of the uncinate process; diffuse indu- ration of pancreas	13,000	135
6	Calcereous pancreatitis with steatorrhea	None	98.6	Normal	No	Yes	.....	.....	125
15	Calcereous pancreatitis with steatorrhea and a diabetic state	None	98.6	Normal	Yes (Mild)	Yes	.....	.....	100
16	Calcereous pancreatitis with steatorrhea and a diabetic state	None	98.6	Slight tenderness	Yes (Mild)	Yes	Diffuse fibrosis of the pancreas; thietal calcifi	.....	90
17	Calcereous pancreatitis with steatorrhea and a diabetic state	Moderate	98.6	Slight tenderness	Yes (Mild)	Yes	Diffuse fibrosis of the pancreas; thietal calcifi	13,000	10

\* In cases 3, 6 and 15 no operation was performed.

† In cases 6, 15 and 16 the count was below 10,000.

in the degree of activity of the pancreatic disease rather than by progressive destruction of the pancreatic acinar tissue.

A normal or lowered amylase level is not incompatible with chronic progressive or recurrent pancreatitis. In 2 of 4 patients with repeated attacks of pain surgical exploration disclosed pronounced induration and fibrosis of the pancreas. The serum amylase values in these patients were not remarkable (table 3, cases 9, 6, 15 and 16). The value may be lowered in the presence of widespread acinar destruction. This was demonstrated in a 62 year old white man in whom marsupialization of a pancreatic cyst had been performed thirty years previously and who had undergone gastroenterostomy twenty years before his admission to the hospital. Steatorrhea had been present for the seven years prior to his admission. The serum amylase level was 40 units. Operation disclosed a diffuse fibrosis and thickening of the pancreas, with dilatation of the pancreatic ducts, which contained many calculi (table 3, case 17).

*Oral Test for Glucose Tolerance.*—The oral test for glucose tolerance was performed in 9 cases. A diabetic type of curve was observed in 8 and a flat curve in 1. The impression was gained from these cases that an elevated curve for glucose tolerance in association with recurrent episodes of pain in the upper part of the abdomen is suggestive of chronic pancreatitis.

The icterus index was increased in 7 of the 9 cases in which it was measured. The values ranged from 10 to 20 in 5 instances. Levels of 158 and 240 were noted for 2 patients, in both of whom the diagnosis of obstruction of the common duct was confirmed at operation. The findings in this series suggest that in addition to disease of the biliary tract chronic pancreatitis also should be considered in the differential diagnosis of obscure recurrent pain in the upper abdominal area associated with jaundice.

*Urine.*—Transitory glycosuria of varying degrees was present in 3 cases. In 1 of these, in which acute abdominal pain, leukocytosis (24,000) and increase of the serum amylase level (1,261 units) were present, the glycosuria subsided after forty-eight hours. In 5 patients with persistent glycosuria a diabetic state was demonstrated in addition to the pancreatitis.

Bilirubinuria in the presence of pancreatitis may indicate severe inflammation, especially of the uncinate process. It was present in 6 patients, in 4 of whom obstruction of the common duct secondary to chronic inflammation of the uncinate process of the pancreas was demonstrated at operation. In the remaining 2 the common duct was patent but the pancreas was diffusely indurated.

*Leukocytosis.*—The leukocyte count was increased in 12 patients, the values ranging from 11,600 to 23,410 and averaging 16,800. Acute active disease was present in 4 of these. It should be noted, however,

that the white blood cell count was normal in 8 patients despite the presence of active pancreatitis. In case 1, in which there were an increased amylase level, recurrent pain and a pancreatic cyst, the count was less than 10,000. In case 2 the leukocyte count was normal in the presence of attacks of pain and severe jaundice. Operation revealed an indurated inflammatory mass involving the head of the pancreas. The patient in case 13, with a history of chills, fever and jaundice, exhibited moderate icterus and loss of weight on admission to the hospital. There was no fever or leukocytosis. At operation the pancreas was indurated but the common bile duct was patent. The leukocyte count was normal in the patient in case 19, who had extensive pancreatic inflammation, an external biliary fistula and a temperature on admission to the hospital of 99.4 F.

#### ROENTGENOLOGIC MANIFESTATIONS

*Cholecystogram.*—There was no constant relationship between the roentgenologic visualization of the gallbladder and the presence of pancreatitis (table 4). Nonvisualization after the oral administration of dye occurred in 5 cases (table 4, cases 6, 7, 14, 17 and 18). A roentgenogram in 1 of these (case 7) demonstrated densities in the right upper area of the abdomen suggestive of cholelithiasis. At operation the gallbladder was distended and adherent to the first portion of the duodenum, but it did not contain calculi. In another (case 14) the gallbladder was normal at operation, but the ampulla of Vater was obstructed by a pancreatic calculus. In a third case (case 17) surgical exploration disclosed a moderately thickened and inflamed gallbladder which contained calculi, while in a fourth (case 18) postmortem examination revealed a thin-walled, apparently normal gallbladder but moderately dilated cystic and common ducts. Thus, in 3 of the 4 patients operated on in whom there was nonvisualization of the gallbladder no primary cholecystic disease was found. Cholelithiasis was noted at operation in 2 of 5 other patients in whom there was normal visualization of the gallbladder (cases 5 and 10). In 1 of these (case 10) fat necrosis was present in the upper part of the abdomen in addition to the induration of the pancreas.

*Gastroduodenal Examination.*—Abnormalities were found in 3 of 13 patients who had gastroduodenal examinations (table 4). The first (case 1) exhibited displacement of the lesser curvature by a mass posterior to the stomach (pancreatic cyst). In the second (case 7) there was dilatation of the stomach and of the first portion of the duodenum, which was due to narrowing of the second portion of the duodenum, by an inflammatory mass involving the uncinate process of the pancreas. In the third patient (case 8) the roentgen examination revealed dilatation of the second portion of the duodenum, demonstrated at operation to be due to an inflammatory process which narrowed the third portion.

*Small Intestine.*—In case 13 roentgenologic studies of the small bowel revealed distention of the loops in the left side of the abdomen. At operation diffuse firm nodular induration of the pancreas was noted, but no mention was made of the intestine. The relationship of a prob-

TABLE 4.—*Roentgenologic Manifestations*

Case	Esophagus	Stomach	Duodenum	Small Bowel	Gallbladder	Pancreatic Calcification
1	Normal	Posterior mass displacing the lesser curvature	Normal	Not examined	Visualized; no calculi	None
2	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
3	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
4	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
5	Not examined	Not examined	Not examined	Not examined	Normal visualization after cholecystostomy	None
6	Normal	Normal	Normal	Not examined	Not visualized	Diffuse calcification
7	Normal	Dilated	Second portion narrowed	Not examined	Not visualized; opaque stones present	Diffuse calcification
8	Normal	Normal	Dilatation of second portion	Not examined	Not examined	None
9	Normal	Normal	Normal	Normal	Not examined	Calcified flecks to the right of the second lumbar vertebra
10	Normal	Normal	Normal	Normal	Visualized; calculi present	None
11	Normal	Normal	Normal	Not examined	Not examined	None
12	Normal	Normal	Normal	Not examined	Not examined	None
13	Normal	Normal	Normal	Dilated loop of jejunum	Not examined	None
14	Normal	Normal	Normal	Not examined	Not visualized	Small calcification to the right of the second lumbar vertebra
15	Normal	Normal	Normal	Not examined	Visualized; no calculi	Diffuse moderate calcification
16	Normal	Normal	Diverticulum of second portion	Normal	Visualized; no calculi	Calcified flecks to the left of the second lumbar vertebra
17	Normal	Functioning gastroenterostomy	Normal	Not examined	Not visualized	Branching calculi to the right of the second lumbar vertebra
18	Not examined	Not examined	Not examined	Not examined	Not visualized	Not examined
19	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
20	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined

able stenotic process of the small intestine to pancreatic inflammation is unknown. (A roentgenogram of the abdomen in 1 case demonstrated distended loops of small bowel suggestive of an obstruction.)

*Pancreatic Calcification.*—Calcifications were found localized in various parts of the pancreas in 4 cases, and they diffusely involved

the organ in 3 others (table 4). There was no uniform pattern in the arrangement of the calcification, and the differentiation between calculi in the ducts and parenchymal calcifications could not be made clinically. Normal visualization of the gallbladder was observed in patients with calcification in the pancreatic ducts as well as in the parenchyma. Two of these (cases 6 and 15), with diffuse calcific changes, manifested steatorrhea and diabetes. However in a third (case 7), in whom there were similar calcifications and a stenosing duodenal lesion, pancreatic function was not changed. In a fourth patient (case 9), with small calcified flecks to the right of the second lumbar vertebra, a cyst of the uncinata process was found at operation, the calcified particles being located in the wall of the cyst. Roentgen study of the fifth patient (case 14) revealed a small indefinite shadow to the right of the first lumbar vertebra. Postmortem examination disclosed a small calculus in Wirsung's duct compressing the common duct. In 2 patients (cases 16 and 17) multiple pancreatic calculi were demonstrated at laparotomy. Pain was a prominent clinical feature in both of these. Diffuse fibrosis, dilatation of the ducts and pancreatic insufficiency were present in each instance.

#### RELATION OF CHRONIC PANCREATITIS TO METABOLIC DISTURBANCES

In 10 patients of the group (50 per cent) mild to significant disturbances in carbohydrate metabolism were found; in 3 (cases 1, 10 and 13) the curves for glucose tolerance were elevated. In 1 (case 1) the curve returned to normal after marsupialization of a pancreatic cyst. Mild diabetes was present in 4 patients (cases 6, 17, 18 and 19). More advanced diabetes was present in 3 (cases 15, 16 and 20). Pancreatic calcifications were present in 4 of the 7 patients with diabetes.

Steatorrhea was present in 5 cases (25 per cent). Pancreatic calcifications were demonstrated in 4 of these, and a diabetic state was present in the entire group. The ages of the patients with steatorrhea ranged from 54 to 75 years, averaging 60 years at the time of their admission to the clinics, in contrast to an average age of 42 years for patients without calcification and steatorrhea.

#### INCIDENCE AND TYPE OF PREVIOUS SURGICAL PROCEDURES

Various surgical procedures (table 5) had been performed previously on 10 patients (50 per cent) of the group in an unsuccessful effort to alleviate the symptoms. Bilateral salpingectomy had been performed on 1 (case 1) and exploratory laparotomy on another for a suspected perforated ulcer. In a third case (case 17) marsupialization of a pancreatic cyst had been done thirty years previously and a gastroenterostomy twenty years before the present admission of the patient to the hospital. In a fourth (case 7) there was a history of an exploratory operation having been carried out ten years earlier.

Operation on the biliary tract had been performed previously in 6 cases. Cholecystectomy had been done in 4. In 3 of these the procedure had been carried out at other institutions and it was not known whether gallstones were present or not. In 2 cases there were no calculi in the gallbladder. Cholecystostomy had been done in 1 case (case 19) and cholecystogastrostomy in another; large solitary gallstones were present in both instances.

#### RELATION OF PREVIOUS OPERATION ON THE BILIARY TRACT TO THE PRESENT OPERATIVE FINDINGS

The interval between the first and the second operation in the 6 patients varied from three months to five years. In 3 the interval was less than one year (cases 14, 19 and 20) and in 3 others less than two years (cases 8, 11 and 13), and in 1 (case 12) it was five years.

The status of the biliary tract, as determined at the second operation, merits further comment (table 6). In case 11 (cholecystectomy had been performed one year previously) the common duct was normal in

TABLE 5.—*Previous Surgical Procedures*

Procedure	Number of Cases
Cholecystectomy.....	4
Cholecystostomy.....	1
Cholecystogastrostomy.....	1
Exploration.....	2
Salpingectomy.....	1
Marsupialization of pancreatic cyst.....	1

size and patent throughout and the pancreas was diffusely indurated. In case 12 (cholecystectomy five years before the patient's admission to the hospital) laparotomy revealed a completely normal common duct; the head of the pancreas was unusually firm and nodular.

The common duct was enlarged in 2 cases. The patient in case 8 had undergone cholecystectomy twenty months before the present operation. The common duct was dilated and measured 2.5 cm. in diameter; however careful probing revealed complete patency of the duct passage into the duodenum. The pancreas again was firm and diffusely indurated. In case 13 cholecystectomy had been performed eighteen months before the patient's admission to the hospital. As in the preceding case, the common duct averaged 2.5 cm. in diameter and was patent throughout and the head of the pancreas was enlarged and indurated. Jaundice had not occurred in these 2 cases.

Operation in case 19 (cholecystostomy four months earlier) disclosed a normal and patent common duct, but the pancreas was firm and indurated as described at the first operation. In case 20 (cholecystogastrostomy five months earlier) adhesions and fibroplasia so involved the portal structures that proper identification was rendered difficult and incomplete.

TABLE 6.—*Diagnosis and Clinical Course in Twenty Patients with Recurrent or Chronic Pancreatitis*

Case	Preoperative Diagnosis	Postoperative Diagnosis	Surgical Procedure	Pathologic Changes Present	Postoperative Course
1	Pancreatic cyst	Pancreatic cyst	Marsupialization of cyst	Grapefruit-sized pseudocyst of the midpancreas	Symptom free—followed for 6 mo.
2	Carcinoma of the head of the pancreas	Interstitial pancreatitis	First stage of pancreaticoduodenectomy; gastroenterostomy and cholecystojejunostomy	Induration of head of pancreas (inflammatory)	Symptoms relieved
3*	Recurrent pancreatitis	.....	.....	.....	.....
4	Perforated peptic ulcer	Pancreatitis, interstitial with edema	Exploration	Edema, induration and slight hemorrhagic areas	Recurrent attacks Attacks gradually decreased but recurred for 2 yr.
5	Cholecystitis and cholelithiasis	Cholecystitis, cholelithiasis, pancreatitis and fat necrosis	Cholecystostomy	Bile-stained turbid fluid around the gallbladder; diffuse fat necrosis; edema of pancreas	No recurrence—followed for 6 yr.
6*	Pancreatic calcification	.....	.....	.....	No change in 3 yr.
7	Duodenal obstruction, cause undetermined	Pancreatitis with induration of uncinate process	Cholecystectomy and posterior gastroenterostomy	Dilatation of the stomach; patulous pylorus, dilated duodenum and dilated common duct; interstitial pancreatitis	Improved—followed for 2 mo.
8	Stone in the common duct	Diffuse interstitial pancreatitis	Cholecystostomy	Common duct dilated but patent throughout; marked diffuse induration of pancreas	Marked improvement, but occasional attack of pain recurred for 6 mo.
9	Stone in the common duct? Carcinoma of the head of the pancreas?	Diffuse interstitial pancreatitis—pseudocyst, head of pancreas	Cyst marsupialized; cholecystojejunostomy	Fist-sized pseudocyst of head of pancreas, dilatation of common duct and diffuse induration of pancreas	Relief of jaundice; no recurrence
10	Cholelithiasis and cholecystitis	Cholelithiasis, diffuse indurative interstitial pancreatitis	Cholecystostomy	Cholelithiasis; fat necrosis; pancreas small and diffusely indurated	No recurrence for 3½ yr.

11	Injury of the common duct, or stone; pancreatitis	Diffuse interstitial pancreatitis	Cholecholestomy	Common duct normal; diffuse induration of the pancreas	No symptoms for 6 mo.
12	Stone in the common duct	Interstitial nodular pancreatitis uncinuate process chiefly involved	Cholecholestomy	Common duct patent; induration and enlargement of uncinuate process	Slight improvement; recurrent attacks
13	Stone in the common duct	Indurative interstitial pancreatitis	Cholecholestomy	Common duct dilated and patent throughout; head of pancreas indurated and enlarged	No improvement
14	Obstruction of the common duct	Obstruction of the common duct; indurative pancreatitis	Cholecholeoduodenostomy	Stone in pancreatic duct below the opening of the common duct, with compression of the duct	Peritonitis; separation of anastomosis; death 10 days post-operatively
15*	Diabetes, steatorrhea and pancreatic calcification	.....	.....	.....	Improved with large doses of pancreatin
16	Diabetes, steatorrhea and pancreatic calcification	Interstitial pancreatitis; pancreatic calculi	Removal of pancreatic calculi	Induration of head of pancreas: 10 to 15 calculi in the pancreatic duct; duct system dilated	Diabetes unchanged; steatorrhea improved 1 year later
17	Obstruction of the pancreatic duct	Cholecystitis and cholelithiasis; pancreatic calculi	Cholecystectomy; removal of pancreatic calculi	Thickened and inflamed gallbladder; dilated pancreatic duct containing many calculi; fibrosis of pancreas	Steatorrhea moderately improved but continued attacks of pain disappeared
18	Cholecystitis with cholelithiasis; coronary thrombosis	Massive suppuration of pancreas (post-mortem)	Autopsy	Autopsy—suppurative pancreatitis, dilatation of common duct and ampulla of Vater, biliary cirrhosis and thrombosis of mesentery and portal veins	Repeated attacks of epigastric pain for 3 mo. prior to death
19	Pancreatitis, chronic cholecystitis and obstruction of the cystic duct	Chronic cholecystitis; chronic pancreatitis	Cholecystectomy and enteroenterostomy	Induration of pancreas; some thickening of gallbladder	Died 6 days later—Friedländer septicemia, acute and chronic pancreatitis and dilatation of pancreatic duct (autopsy)
20	Carcinoma of pancreas, with metastases	Chronic pancreatitis; hyperplastic peritonitis	Exploration	Diffuse inflammatory mass	Died 18 days postoperatively

\* In cases 3, 6 and 15 no operation was performed.



The unusual dilatation of the common duct, without obstruction, observed in cases 8 and 13 is of interest and may represent an adaptation by the choledochus to the function of the gallbladder. It is to be noted, however, that in 2 other cases, referred to previously, the common ducts were normal after cholecystectomy. The interval between cholecystectomy and the dilatation of the duct seems to be of little importance, for the dilated bile ducts were found twenty and eighteen months after operation in cases 8 and 13 while in cases 11 and 12 normal ducts were found twelve and sixty months after removal of the gallbladder. No explanation can be offered for these variable findings. The mechanism of dilatation of the common duct after cholecystectomy has been the subject of considerable investigation. Rothman,<sup>5</sup> in a review of the mechanism of pain after cholecystectomy, found evidence of a disturbed choledochal sphincter in some instances. After cholecystectomy the common duct has been shown to dilate as the sphincter muscle, because of hypertonicity and hypertrophy, intermittently retards the flow of bile. The role of the pancreatitis in the production of dilatation is obscure. Conceivably in some cases both may result from the same mechanism, i.e., a disturbance in the sphincter of Oddi with a "common channel." However the absence of dilatation of the common duct in 2 patients with pancreatitis does not support this hypothesis.

#### SURGICAL PROCEDURES AND RESULTS

Surgical exploration was performed in 16 of the 20 patients. The operative procedures are listed in table 7. Drainage of the common duct or of the gallbladder was performed in 6; anastomosis of the common duct or gallbladder to the intestinal tract was accomplished in 3.

Obstruction of the common duct with jaundice following chronic induration or fibrosing pancreatitis is an infrequent finding. It was present in 2 cases of the series. Cholecystojejunostomy relieved the obstruction in both cases. Peterson and Cole<sup>6</sup> report obstruction in 3 cases. Walters, in a study of 80 patients with stricture of the common duct, found that in none was the condition due to pancreatitis while in 1 it was secondary to a calcified pancreatic cyst.<sup>6</sup>

#### COMMENT

The present analysis indicates certain clinical aspects which may be of importance in the diagnosis of recurrent pancreatitis.

Bouts of severe pain in the upper abdominal area are noted in almost all patients. These tend to recur over a prolonged period, which

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5. Rothman, M. M., in Bockus, H. L.: *Gastroenterology*, Philadelphia, W. B. Saunders Company, 1946, vol. 3, pp. 514-530.

6. Peterson, L. W., and Cole, W. H.: Chronic Sclerosing Pancreatitis Causing Stenosis of the Common Bile Duct, *Arch. Surg.* 51:15-21 (July) 1945.

averaged four years in 60 per cent of the present series. The duration of the disease prior to diagnosis has been reported by others to vary from five to seven years. The pain is usually sharp and unremitant, and sometimes it is boring. Characteristically, it is prolonged, lasting three hours or more, and little or no relief is obtained from opiates. Radiation of pain is frequently present but without a definite pattern of distribution. The initial diagnoses are shown in table 6, as are the operative findings and the postoperative course.

In approximately 50 per cent of cases a previous laparotomy has been performed which failed to relieve the symptoms or establish the diagnosis. The importance of considering the possibility of pancreatitis in the treatment of patients with pain in the upper part of the abdomen following operation on the biliary tract is evident. The value of careful exploration of the pancreatic region in patients with a syndrome suggestive of biliary colic in whom laparotomy fails to disclose gallstones is to be emphasized.

TABLE 7.—Operative Results in Chronic Pancreatitis

Operation	Cases	Relieved	Im- proved	No Change	Deaths
Marsupialization of pancreatic cyst.....	1	1	..	..	..
Marsupialization and cholecystojejunostomy.....	1	1	..	..	..
Gastroenterostomy and cholecystojejunostomy..	1	1	..	..	..
Exploration .....	2	..	..	1	1
Cholecystostomy .....	2	2	..	..	..
Cholecystectomy and posterior gastroenterostomy	1	1	..	..	..
Cholecystectomy and enteroenterostomy.....	1	..	..	..	1
Choledochostomy .....	4	1	1	2	..
Choledochoduodenostomy .....	1	..	..	..	1
Removal of pancreatic calculi.....	1	..	1	..	..
Removal of pancreatic calculi and cholecystectomy	1	..	1	..	..
	16	7	3	3	3

The difficulty of differentiating between benign and neoplastic pancreatic lesions may be great, since 35 per cent of the present series had abdominal pain, loss of weight and jaundice, symptoms frequently noted in carcinoma. Musser<sup>7</sup> reported pain to be the chief complaint in 100 cases of carcinoma of the pancreas without jaundice. Colic-like pain was present, with involvement of the pancreatic ducts, and pain in the back with involvement of the body and tail of the pancreas. Pain in the left upper abdominal area was not infrequent in the presence of pancreatitis.

Jaundice of varying degree may occur in chronic pancreatitis in the absence of obstruction of the common duct, an observation made in 4 patients. In 3 others the common duct was obstructed by an indurated fibrotic inflammatory process of the head of the pancreas. Walters and Dehne<sup>7</sup> found that 15 per cent of 113 patients with jaundice due to obstruction of the common duct secondary to lesions of the pancreas

7. Musser, J. H., cited by Walters, W., and Dehne, E. A.: Jaundice Caused by Pancreatic Lesions, Surg., Gynec. & Obst. 54:832-835, 1932.

survived for five years or more, which indicated that the lesion was benign. In 99 of the 113 the jaundice was painless.

Certain laboratory procedures are of value in the differential diagnosis. A persistent increase in the blood sugar level, such as is noted in diabetes, is frequently observed after a glucose tolerance test.

Our limited experience confirms the generally accepted importance of high amylase levels in the diagnosis of pancreatic disease, especially during the acute episodes. Two patients with increased amylase levels had decided pancreatic induration at operation. It is important to realize, however, that the presence of a normal or lowered amylase content is not incompatible with active pancreatic disease, as was demonstrated in 5 cases in which the diagnosis was confirmed at operation. Elman<sup>8</sup> has found experimentally that the blood amylase content may double within fifteen minutes, quadruple in an hour and reach a level which is twenty times the normal one within twenty-four hours after complete obstruction of the pancreatic duct. Indeed, even simple palpation of the pancreas during operation may cause a transient but definite increase in the amylase level. In acute transient pancreatitis increased amylase values have been found at the height of the attack, with a return to normal as the process subsided. A rise in the amylase level followed by abnormally low levels has been observed in acute necrosis of the gland. Increased amylase values may indicate obstruction of the pancreatic duct, while lowered levels may suggest destruction of acinar tissue. Walters and Cleveland<sup>9</sup> report the serum amylase and lipase contents to be of diagnostic value during the first seven to ten days after an attack of pancreatitis; the amylase content returns to normal sooner than the lipase content. Comfort and others<sup>3</sup> found the serum amylase to be increased during acute attacks in 8 patients and between attacks in 3 among a group of 22. Variations between 60 and 150 units (Somoygi) have been considered normal for the serum amylase level at the University clinics. Levels below 50 and above 200 are suggestive of pancreatic disease but are not conclusive.

Roentgenograms of the upper part of the gastrointestinal tract may demonstrate constriction of the duodenum by fibrosing pancreatic lesions and displacement of the lesser curvature by a pancreatic cyst. Metheny and others<sup>10</sup> have described changes consisting of pressure on the greater curvature, duodenal ileus and enlargement of the duodenal loop during episodes of acute pancreatitis. They suggest that they are

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8. Elman, R.: The Diagnosis and Treatment of Acute Non-Hemorrhagic Pancreatitis, *Am. J. Digest. Dis.* **4**:732-736, 1938.

9. Walters, W., and Cleveland, W. H.: Surgical Lesions of the Pancreas: A Review, *Arch. Surg.* **42**:819-838 (May) 1941.

10. Metheny, D.; Roberts, E. W., and Stranahan, A.: Acute Pancreatitis with Special Reference to X-Ray Diagnosis, *Surg., Gynec. & Obst.* **79**:504-508, 1944.

related to edema of the pancreas, which may enlarge to three times its normal size.

Pancreatic calculi are present in approximately one third of the patients with chronic pancreatitis and are readily demonstrated by a simple roentgenogram of the upper part of the abdomen. Ductal calcifications often are larger and more definite than diffuse parenchymal calcifications, attaining a diameter of 1 cm. or more. The differentiation between ductal and parenchymal calcifications is, however, usually not possible clinically. Pasternack<sup>11</sup> has noted that pancreatic calcification may form in less than one to two years.

An increased incidence of steatorrhea and of the diabetic state in pancreatitis and pancreatic calculi is noted in 25 to 50 per cent of the cases. Haggard and Kirtley<sup>12</sup> found glycosuria in 9.2 per cent of patients with pancreatic calculi. Pasternack reported diabetes in 50 per cent of patients with calcifications, while Snell and Comfort<sup>13</sup> noted diabetes in 8 and fatty diarrhea in 8 of a total of 18 patients. Pancreatic calcification was noted at autopsy in 5 of 16,000 patients by King and Waghelstein.<sup>14</sup> Pascucci,<sup>15</sup> in a review of 117,031 autopsies, recorded 52 cases (0.044 per cent) of pancreatic calculi. Pancreatic cysts were present in 0.061 per cent of 29,487 patients at autopsy. The cysts did not appear to be the sequela of calculi.

The value of cholecystectomy in the presence of pancreatitis requires further consideration. Removal of the gallbladder usually does not relieve the symptoms. Behrend,<sup>16</sup> in discussing the relationship of chronic pancreatitis to disease of the common duct, stated that cholecystoduodenostomy is the procedure of choice for patients with recurrent colic who at operation are found to have a noncalculous gallbladder. Vuori<sup>17</sup> found acute pancreatitis in 4 patients who had been subjected to cholecystectomy one and a half to four years earlier. In a study of 46

11. Pasternack, J. G.: Report of Three Cases of Calcareous Pancreatitis with Autopsies, *Ann. Int. Med.* **19**:757-767, 1943.

12. Haggard, W. D., and Kirtley, J. A., Jr.: Pancreatic Calculi: A Review of Sixty-Five Operations and One Hundred and Thirty-Nine Non-Operative Cases, *Ann. Surg.* **109**:809-826, 1939.

13. Snell, A. M., and Comfort, M. W.: The Incidence and Diagnosis of Pancreatic Lithiasis: Review of Eighteen Cases, *Proc. Staff Meet., Mayo Clin.* **17**: 209-211, 1942.

14. King, A. B., and Waghelstein, J. M.: Calcification of the Pancreas, *Arch. Int. Med.* **69**:165-176 (Feb.) 1942.

15. Pascucci, L. M.: Pancreatic Cysts and Lithiasis, *Am. J. Roentgenol.* **52**: 80-87, 1944.

16. Behrend, M.: Diseases of the Common Bile Duct and Their Relation to the Gastrointestinal Tract with Special Reference to the Role of Chronic Pancreatitis, *J. A. M. A.* **116**:204-208 (Jan. 18) 1941.

17. Vuori, E. O.: Four Cases of Acute Pancreatitis in Four Cholecystectomized Patients: Recurrence in Forty-Six Cases of Acute Pancreatitis, *Acta chir. Scandinav.* **88**:220-226, 1943.

cases of acute pancreatitis, he made a comparative analysis regarding recurrence or chronicity in patients who had undergone cholecystectomy and in those on whom this operation had not been performed. He concluded that cholecystectomy is of little prophylactic importance either in the primary or in the recurrent condition.

Surgical intervention gives good results in patients with obstruction of the common duct and in those with constriction of the duodenum. Removal of ductal calculi frequently relieves pain, while steatorrhea may be favorably affected. An established diabetic state tends to remain unaltered.

#### SUMMARY

In a group of 20 patients with chronic pancreatitis there were 12 men and 8 women. Fifty per cent were below 50 years of age.

Symptoms had been present for less than one year in 40 per cent; in the remaining 60 per cent the average duration was four years.

Recurrent bouts of severe pain in the upper abdominal area constituted the chief complaint in 85 per cent of the group.

The physical findings were indefinite and noncontributory. Jaundice of varying degree was present in 25 per cent of the patients.

The serum amylase content, determined in 8 patients, was increased in 3, normal in 4 and decreased in 1.

The oral test for glucose tolerance, carried out in 9 instances, yielded a diabetic type of curve in 8 and a flat curve in 1.

Pancreatic calcifications were demonstrated roentgenologically in 35 per cent of the cases.

Disturbances of carbohydrate metabolism were present in 10 of the 20 patients, a mild diabetic state being found in 4 and a more severe type in 3. In the remaining 3 glycosuria was transitory.

Steatorrhea was present in 25 per cent of the group.

Half of the patients had had previous surgical treatment, without relief of the abdominal pain.

#### CONCLUSIONS

1. Recurrent pancreatitis tends to pursue a prolonged and chronic course.

2. The condition is characterized by repeated bouts of severe pain in the upper part of the abdomen.

3. A diabetic type of curve following the oral test for glucose tolerance in the presence of such bouts suggests the presence of pancreatitis.

4. Pancreatic calcifications are not infrequently found roentgenologically.

5. Disturbances of carbohydrate metabolism are frequent.

6. Steatorrhea is not uncommon.

7. The possibility of pancreatitis must be especially considered in cases in which the patient continues to have attacks of pain simulating that of biliary colic after cholecystectomy has been performed.

# ACUTE MEGAKARYOCYTIC LEUKEMIA

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THERE have been many observations in medical literature in which megakaryocytes have been described as a prominent feature in pathologic conditions of the blood. The number of these cells is frequently increased in thrombocythemia and polycythemia vera. Their presence in the bone marrow, liver, spleen and other viscera has been mentioned in numerous articles on myelogenous leukemia and various other diseases. Although the classification of leukemias by most American authors, including Bethell,<sup>1</sup> Downey,<sup>2</sup> Forkner,<sup>3</sup> Kolmer,<sup>4</sup> Kracke,<sup>5</sup> Osgood,<sup>6</sup> Levin<sup>7</sup> and Wintrobe,<sup>8</sup> recognizes the possibility of megakaryocytic leukemia, the specific criteria necessary for such a diagnosis are not stated in detail.

Von Boros and Korényi<sup>9</sup> reported a condition in 1931 which they designated as "acute megakaryoblastic leukemia," but the authenticity of the case has been questioned by American hematologists owing to lack of sufficient data.

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1. Bethell, F. H.: Leukemia: The Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy, *Ann. Int. Med.* **18**:757 (May) 1943.

2. Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 1273.

3. Forkner, C. E.: *Leukemia and Allied Diseases*, New York, The Macmillan Company, 1938.

4. Kolmer, J. A.: *Clinical Diagnosis and Laboratory Examination*, New York, D. Appleton-Century Company, Inc., 1944, p. 689.

5. Kracke, R. R., and Gower, H. E.: *Diseases of Blood and Atlas of Hematology*, Philadelphia, J. B. Lippincott Company, 1937, p. 304.

6. Osgood, E. E., and Ashworth, C. M.: *Atlas of Hematology*, San Francisco, J. W. Stacy, Inc., 1937, p. 145.

7. Levin, V., in discussion on papers of Kracke and Graver, Rosenthal and Harris and Haden, *J. A. M. A.* **104**:709 (March 2) 1935.

8. Wintrobe, M. M.: *Clinical Hematology*, ed. 2, Philadelphia, Lea & Febiger, 1946, p. 703.

9. von Boros, J., and Korényi, A.: Ueber einen Fall von akuter Megakaryoblastenleukämie, zugleich einige Bemärkungen zum Problem der akuten Leukämie, *Ztschr. f. klin. Med.* **118**:697, 1931.

Lindeboom<sup>10</sup> in 1938 noted that giant cells of megakaryocytic type were prominent features in a group of cases of a disorder designated as "aleukemic megakaryocytic leukemia" and suggested that this should be considered as a disease entity.

Kopäc<sup>11</sup> reviewed the German literature in 1943 and presented a case in which giant cells were present in leukemia. He concurred with the authors Körner,<sup>12</sup> Matthaeus<sup>13</sup> and Wienbeck<sup>14</sup> that the giant cells were basically megakaryocytes, even though other German authors, including Barth,<sup>15</sup> Matousek,<sup>16</sup> Krondel,<sup>17</sup> Esbach<sup>18</sup> and Dubinskaja,<sup>19</sup> considered them to be identical with reticuloendothelial cells.

The case that Barth reported has since been disregarded because the disease therein was spoken of as "endotheliosis with myelogenous leukemia."

Previous cases cited as instances of megakaryocytic leukemia and the case presented here are not to be confused in the nosologic system with cases classified under the following titles: myeloid megakaryocytic hepatosplenomegaly,<sup>20</sup> aleukemic myelosis with osteosclerosis,<sup>21</sup> megakaryocytic myelosis with osteosclerosis,<sup>22</sup> chronic nonleukemic myelosis<sup>23</sup> and leucoerythroblastic anemia with myelosclerosis.<sup>24</sup>

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10. Lindeboom, G. A.: Ueber die sogenannte aleukämische megakaryocytäre Myelose, *Acta med. Scandinav.* **95**:388, 1938.

11. Kopäc, Ueber die Bedeutung der Megakaryocyten-Leukämien, *Virchows Arch. f. path. Anat.* **310**:3 (July) 1943.

12. Körner, K.: Auffallende Riesenzellenbefunde bei akuten Myeloblastenleukämie, *Virchows Arch. f. path. Anat.* **259**:617, 1926.

13. Matthaeus, H.: Zur Kenntnis der Riesenzell-Leukämien, *Beitr. z. path. Anat. u. z. allg. Path.* **101**:189, 1938.

14. Wienbeck, J.: Die menschlich Leukämie, Jena, Gustav, Fischer, 1942; cited by Kopäc.<sup>11</sup>

15. Barth, H.: *Virchows Arch. f. path. Anat.* **356**:693, 1925; cited by Kopäc.<sup>11</sup>

16. Matousek, V.: *Beitr. z. path. Anat. u. z. allg. Path.* **106**:332, 1942; cited by Kopäc.<sup>11</sup>

17. Krondel, A.: *Beitr. z. path. Anat. u. z. allg. Path.* **106**: 332, 1942; cited by Kopäc.<sup>11</sup>

18. Esbach, H.: *Virchows Arch. f. path. Anat.* **303**:706, 1939; cited by Kopäc.<sup>11</sup>

19. Dubinskaja, B.: Ueber die Riesenzellenformen der Myelose, *Virchows Arch. f. path. Anat.* **270**:192, 1928.

20. Downey, H., and Norland, M.: Hematologic and Histologic Study of a Case of Myeloid Megakaryocytic Hepato-splenomegaly, *Folia haemat.* **62**:1, 1939. Chini, V.: La mielosi aleucemica megacariocitaria, *Policlinico (sez. med.)* **43**:257 (June) 1936.

21. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, *Ann. Int. Med.* **6**:1087 (Feb.) 1933. Lindeboom.<sup>10</sup>

22. Hower, T. F.: Megakaryocytic Myelosis with Osteosclerosis, *J. Path. & Bact* **45**:383 (Sept.) 1937.

It is not in the realm of this paper to discuss either the origin and maturation of the megakaryocytes or the cause of leukemia. We shall, however, present a case because it demonstrates the following unusual and interesting features: (1) absence of splenomegaly and lymphadenopathy; (2) slight hepatomegaly; (3) absence of osteosclerosis and osteofibrosis; (4) no history or evidence of a chronic granulomatous disease or of exposure to drugs; (5) marked anemia, with presence of numerous immature erythrocytes; (6) leukopenia, with immature myeloid cells; (7) thrombopenia, with atypical platelets; (8) erythromyelomegakaryocytic hyperplasia of the bone marrow, and (9) evidence at necropsy of extramedullary megakaryocytic infiltrations into other viscera. After careful analysis of the case to be presented, it is apparent that the condition does not fit into the aforementioned categories of disease and therefore necessitates a revision of the classification of leukemia to include megakaryocytic leukemia, not as a possibility, but as a clinical entity.

As far as we can determine, this is the first such case to be reported in the American literature.

#### REPORT OF A CASE

D. M., a 66 year old white married man, an actor, was first seen in the clinic early in 1936. He was born in Scotland. His father died at 70 years of age of unknown cause. His mother died at 68 years of cancer of the stomach. His childhood illnesses were of the usual variety and irrelevant to the present illness.

His first visit to the clinic was for epistaxis, which was a local problem and responded to cauterization. At this time he stated that his general health had always been excellent. He was a small man and prided himself on his physical prowess, having been a professional tumbler at one time.

In February 1941 he was admitted to the Hollywood Presbyterian Hospital for treatment of lobar pneumonia. He responded to sulfathiazole therapy and was discharged at the end of one week. At this time laboratory findings were within normal limits (table 1).

In January 1943 the patient was again admitted to the hospital for approximately one week, with a clinical diagnosis of bronchopneumonia, which responded readily to therapy.

In May 1946 he was seen in the clinic for pain on movement of his neck. He attributed this pain to the possibility of a slight injury and stated that he had been "pushed around a bit while attempting to pass a picket line." The physical condition

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23. Favre, M.; Croizat, P., and Guichard, A.: La myélose aleucémique mégakaryocytaire: Contribution à l'étude des syndromes hépato-spléniques, *Ann. de méd.* **35**:5 (Jan.) 1934; abstracted, *J. de méd. de Lyon* **14**:753 (Dec. 20) 1933. Mettier, S. R., and Rusk, G. Y.: Fibrosis of the Bone Marrow Associated with a Leukemoid Blood Picture, *Am. J. Path.* **13**:377 (May) 1937. Carpenter, G., and Flory, C. M.: Chronic Non-Leukemic Myelosis, *Arch. Int. Med.* **67**:489 (March) 1941. Hickling, R. A.: Chronic Non-Leukemic Myelosis, *Quart. J. Med.* **6**:253 (July) 1937.

24. Vaughan, J., and Harrison, G. V.: Leuco-Erythroblastic Anemia and Myelosclerosis, *J. Path. & Bact.* **48**:339 (March) 1939.



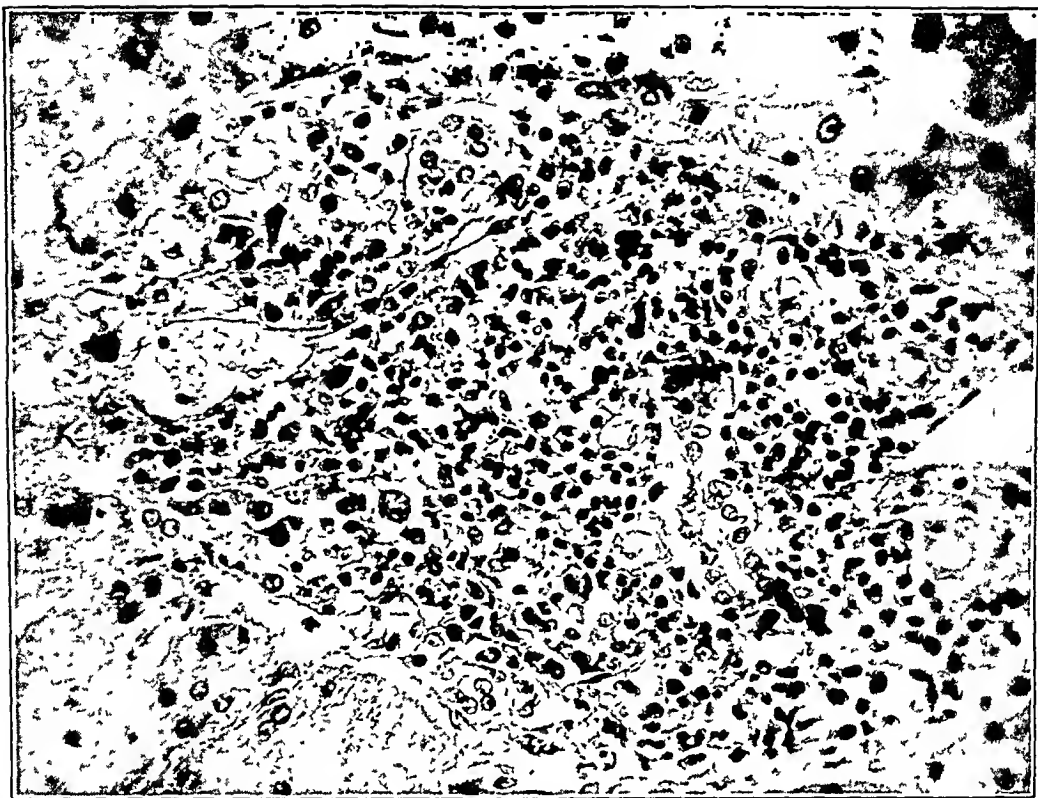


Fig. 1.—Photomicrograph of the liver, showing infiltrations into the periportal spaces with leukemic cells and megakaryocytes.  $\times 180$ .

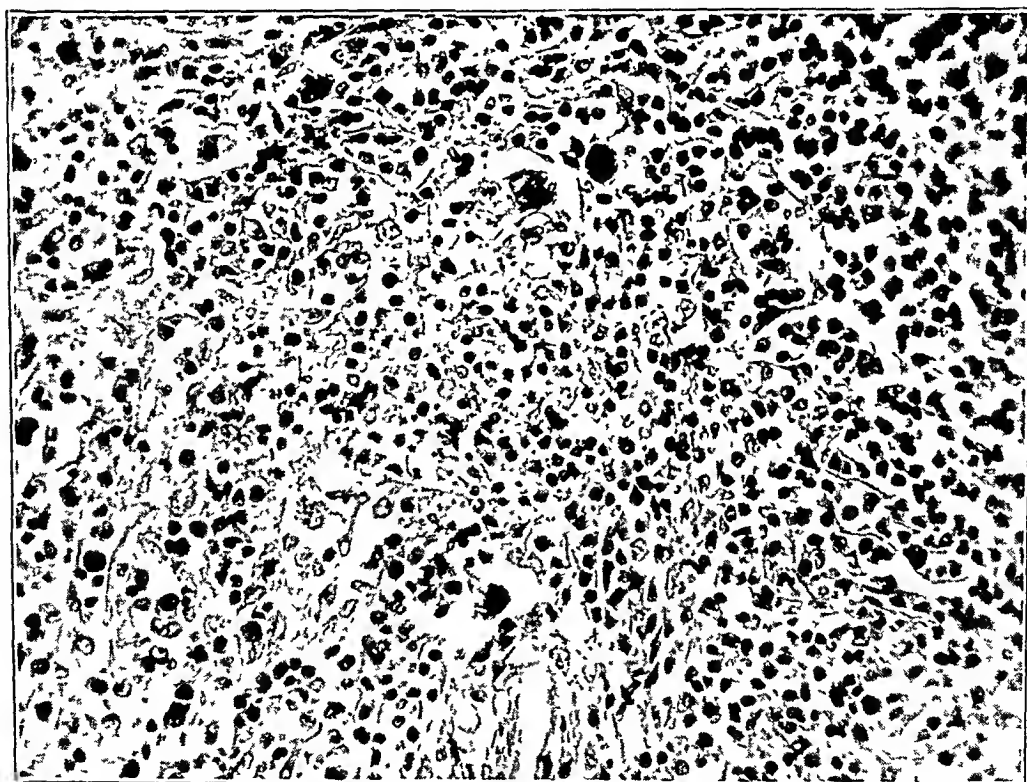


Fig. 2.—Photomicrograph of the spleen. The sinuses are dilated and contain numerous megakaryocytes, immature myeloid cells and erythroid cells  $\times 180$ .

TABLE 1.—Blood Counts of a Patient with Megakaryocytic Leukemia

Date	Red Blood Cell Count	Hemo- globin, %	White Blood Cell Count	Blasto- cytes	Pro- myelo- cytes	Myelo- cytes	Meta- myelo- cytes	Neu- tro- phils	Non- tro- phils	Eosino- phils	Baso- phils	Lym- pho- cytes	Mono- cytes	Un- classi- fied	Megalo- blasts	Early Eryth- ro- cytes	Late Eryth- ro- cytes	Normo- blasts	Comments
<b>First admission</b>																			
2/24/41	3,840,000	69	20,950	..	..	..	..	..	76	..	..	23	1	..	..	..	..	..	Coagulation time, 3 min.
2/25/41	4,230,000	62	15,080	..	..	..	..	..	89	1	..	9	1	..	..	..	..	..	..
3/ 1/41	3,810,000	66	10,500	..	..	..	..	..	72	2	1	22	3	..	..	..	..	..	..
<b>Second admission</b>																			
1/27/43	4,750,000	..	21,000	..	..	..	..	15	33	..	..	12	10	..	..	..	..	..	Coagulation time, 4½ min.
2/19/43	4,650,000	90	9,800	..	..	..	..	..	69	..	..	30	1	..	..	..	..	..	..
7/ 2/46	2,300,000	68	6,000	..	..	..	..	..	50	3	..	45	2	..	..	..	..	..	Slight achro- masia
8/13/46	2,950,000	70	.....	..	..	1	..	..	65	15	..	20	..	..	..	..	..	..	Occa- sional achromasia and polychromasia;
8/16/46	2,130,000	55	.....	..	..	..	..	..	65	..	..	..	..	..	..	..	..	..	occasional macrocytes
8/23/46	2,320,000	62	3,950	..	..	..	..	..	47	2	..	50	..	..	..	..	..	8	Same as above
9/ 3/46	3,480,000	70	4,850	..	..	1	..	..	14	3	2	48	2	..	..	..	..	..	Achromasia and polychromasia
10/ 1/46	2,810,000	75	.....	..	..	..	..	..	32	..	..	..	..	..	..	..	..	..	Anisocytosis, polychromasia and polkilo- cytosis
10/ 8/46	2,400,000	68	1,850	..	..	2	..	..	32	7	..	58	..	..	..	..	..	..	..
<b>Third admission</b>																			
11/ 3/46	2,250,000	44, or 7 Gm.	6,350	16	12	11	10	11	10	5	..	..	..	2	3	3	12	11	Coagulation time, 3¼ min.; bleeding time, 3 min.; diffuse basophilia
11/ 6/46	2,550,000	47, or 7.1 Gm.	5,116	17	8	Eosino- phils; tro- phils	Neu- tro- phils	Neu- tro- phils	9	11	0.6	21	0.4	2	2	7	10	10	Total eosino- phils, 36%; marked regen- eration of red blood cells
11/11/46	3,310,000	60	6,100	12	3	5	5	15	15	19	..	21	1	..	4	8	3	6	Platelets, 82,000
11/14/46	1,930,000	31.9	5,900	19	6	2	2	1	1	19	..	10	1	7	3	1	2	1	Platelets, 78,000
11/16/46	1,520,000	24	6,438	24	4	6	1	5	2	21	..	35	1	6	3	5	3	7	..

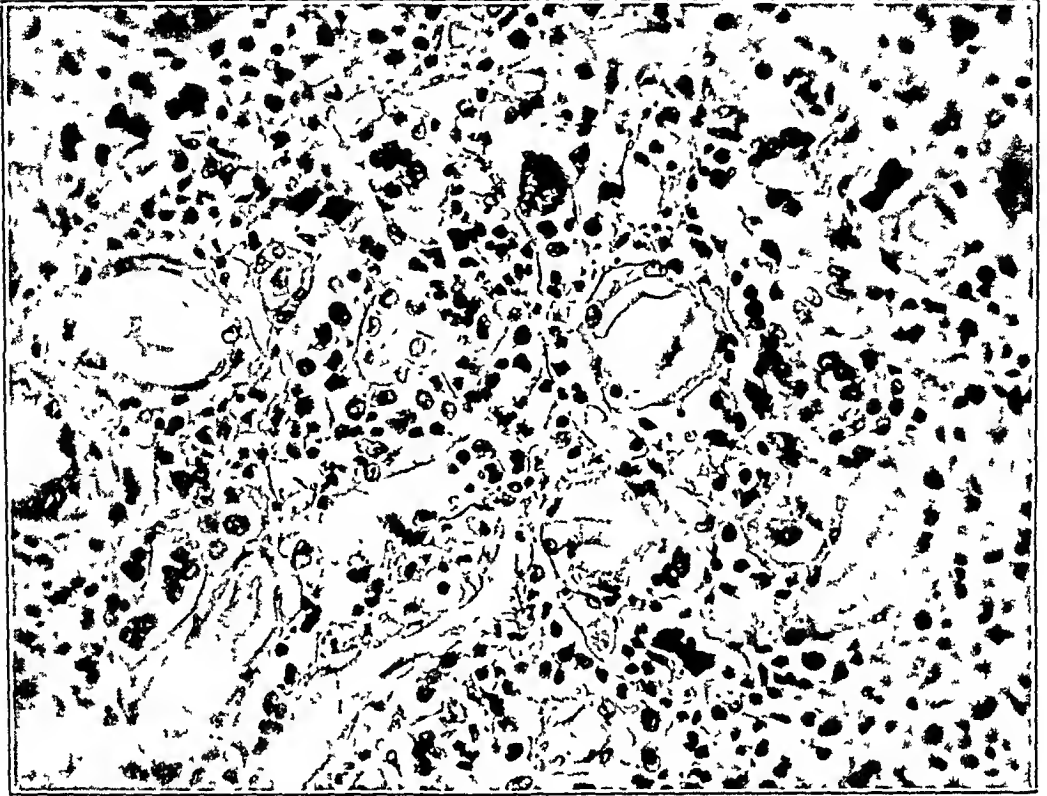


Fig. 3.—Photomicrograph of the kidney, showing numerous megakaryocytes and leukemic infiltrations into the parenchyma  $\times 180$ .

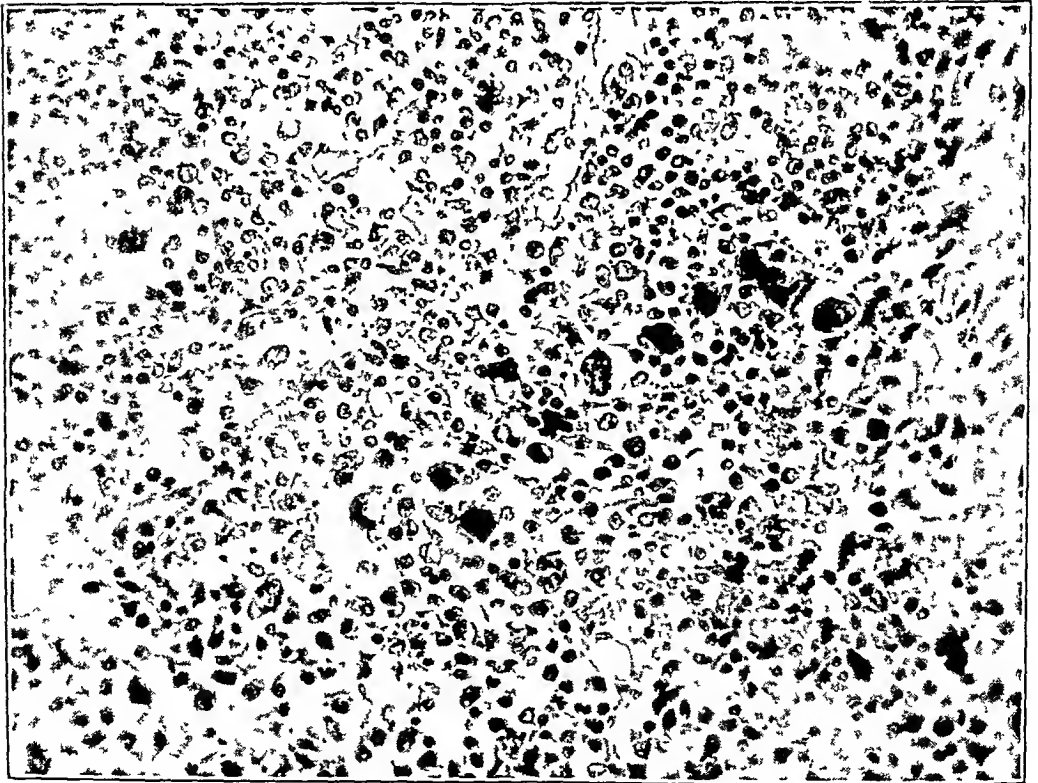


Fig. 4.—Photomicrograph of a lymph node. The architecture has been distorted with numerous megakaryocytes, myeloblasts and megaloblasts  $\times 180$ .

at this time was essentially normal except for limited motion of the neck on all rotary movements. Roentgenographic studies of the cervical region of the spine revealed advanced cervical arthritic changes, with extreme lipping, bridging and narrowing of the cartilages. He was treated with diathermy, massage and salicylates, and the pain subsided.

He returned to the clinic in July 1946, complaining of easy fatigability, some shortness of breath on exertion and nocturia. The pain in his neck had greatly improved. The positive findings on physical examination at this time were slight limitation of the movements of the neck, a systolic murmur at the apex of the heart, a palpable liver enlarged about 2 fingerbreadths below the costal margin and a moderately enlarged but soft prostate gland. Laboratory procedures revealed moderate anemia. Urinalysis, serologic tests and determination of the nonprotein nitrogen content gave normal results. He was given liver extract and folic acid, which produced a slight change in the blood picture during August and September (table 1). The gastrointestinal tract was essentially normal except for a few diverticula in the sigmoid colon. An orthocardiogram demonstrated calcification of the aortic commissure and slight hypertrophy of the left ventricle. The electrocardiogram was normal.

On Nov. 3, 1946, signs and symptoms of acute myocardial failure developed. At this time the patient was readmitted to the hospital. Physical examination revealed a well developed, well nourished, pale man, 66 years of age, with extreme orthopnea and evidence of peripheral edema. His blood pressure was 146 systolic and 76 diastolic, the temperature 99 F., the pulse rate 72 and regular and the respirations 16. The head was normal except for notable pallor of the conjunctiva and buccal mucosa. The neck was normal except for evidence of increased venous pressure. There was no lymphadenopathy in the neck or in the axillary or inguinal regions. The chest was emphysematous. Auscultation revealed fine crepitant rales at the bases of both lungs. The heart was enlarged to both the right and the left, the apex being 2 cm. beyond the midclavicular line. A loud systolic murmur was heard over the mitral area. The rhythm was regular. The liver was enlarged 2 fingerbreadths below the costal margin in the midclavicular line. The spleen was not palpable. There was moderate pitting edema of both ankles. The reflexes were normal, as were the external genitalia. The prostate gland was moderately enlarged and soft.

*Special Studies.*—The blood counts are recorded in table 1. On the patient's admission to the hospital the total number of erythrocytes was 2,250,000 per cubic millimeter. The hemoglobin content was 7 Gm. per hundred cubic centimeters. The leukocyte count was 6,350 per cubic millimeter. The differential count was as follows: blastocytes, 16 per cent; promyelocytes, 12 per cent; metamyelocytes, 10 per cent; neutrophilic nonfilaments, 11 per cent; neutrophilic filaments, 10 per cent, and unclassified cells, 2 per cent. There was notable regeneration of the erythrocytes, including 3 megaloblasts, 12 late erythroblasts and 11 normoblasts. Ovalocytes, tailed forms, Howell-Jolly bodies and polychromatophilia were present. At this time a diagnosis of aleukemic myeloid leukemia was made.

Studies of sternal bone marrow obtained by needle aspiration five days after the patient's admission showed increased cellularity, involving all myeloid elements, megakaryocytes and erythroid series. The differential count of the marrow cells is given in table 2. The myelogenic erythrogenic ratio was 2 to 3. There was a relative decrease in the myeloid elements and an absolute increase in the erythroid elements, with eosinophilia. The most bizarre changes were in the early megakaryocytes. They were readily found, and immature forms predominated. Of 100

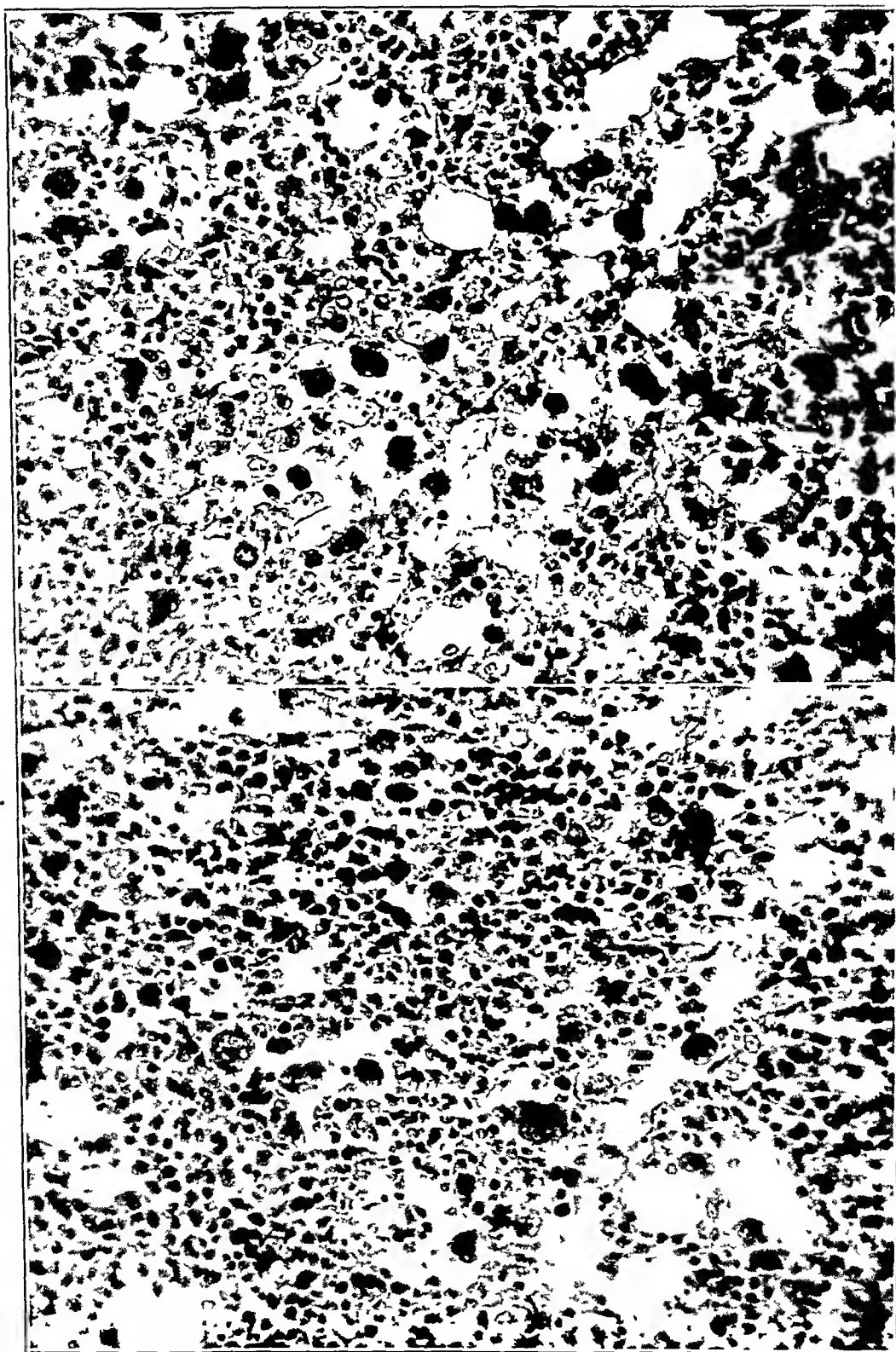


Fig. 5.—Photomicrographs of the sternum (upper figure) and ribs (lower figure), showing hyperplasia of all elements, especially the megakaryocytes.  $\times 180$ .

megakaryocytes, 72 per cent were early forms, 20 per cent were intermediate forms and 8 per cent were mature forms.

Slides of the peripheral blood and bone marrow were submitted to Dr. L. W. Diggs,<sup>25</sup> of the Cleveland Clinic Foundation, who suggested "the possibility of megakaryocytic leukemia as a suitable term for this picture if supported by further evidence of metastatic giant cells in other viscera"; this opinion was later confirmed. Dr. Verne Mason,<sup>26</sup> of the University of Southern California, and Dr. John H. Lawrence,<sup>27</sup> of the University of California, concurred with the opinion that the case presented many unusual features. Mason described it as "atypical myeloblastic leukemia with an eosinophilic response—a very rare type of leukemia," while Lawrence suggested that it be classified as "atypical myeloid leukemia, megakaryocytic type."

Roentgenograms were made on various occasions from 1941 to 1946. At no time were there demonstrable changes in the architecture of the bones except for advanced degenerative arthritic changes, with extreme lipping, bridging and narrowing of the cartilages of the cervical region of the spine. Gastrointestinal studies in August 1946 were noncontributory. The results of electrocardiographic studies made in 1941 and 1946 were within normal limits, and reactions to serologic tests

TABLE 2.—*Differential Count of the Bone Marrow Cells*

Early nucleus without cytoplasm.....	2.4	Plasma cells.....	0.2
Stem cells—undifferentiated.....	6.4	Monocytes.....	0.6
Promyelocytes.....	3.8	Reticuloendothelial cells.....	4.6
Eosinophilic myelocytes.....	8.6	Megakaryocytes.....	1.4
Eosinophilic metamyelocytes.....	4.4	Mitotic figures.....	0.4
Eosinophilic nonfilaments.....	2.2	Megaloblasts.....	2.2
Eosinophilic filaments.....	3.6	Early erythroblasts.....	8.0
Neutrophilic metamyelocytes.....	1.0	Late erythroblasts.....	19.8
Neutrophilic nonfilaments.....	0	Normoblasts.....	21.6
Neutrophilic filaments.....	0.2	Mitotic figures.....	2.8
Lymphocytes.....	2.8		

were repeatedly negative from 1937. The patient's blood was type B-III, Rh negative.

The nonprotein nitrogen content on July 24, 1946, was 36.5 mg. (not fasting). The fasting levels on November 11 and 13 were 70.5 and 63.2 mg. respectively. The urea nitrogen on November 16 was 42.8 mg. per hundred cubic centimeters of blood. The prothrombin time (Quick's method), taken on November 11, was 96 per cent normal. On November 13 the bleeding time was two minutes and the coagulation time was three to four minutes.

The urine was consistently normal until the patient's terminal illness. On November 6 the specific gravity was 1.018, the reaction was alkaline, traces of sugar and of albumin were present and microscopic examination showed occasional hyaline casts, with 2 to 5 leukocytes per high power field. On November 16 the specific gravity was 1.014, the reaction was acid, albumin was present (3 plus) and numerous coarsely granular casts were present.

*Course in Hospital.*—Treatment at the time of the patient's admission to the hospital was for acute myocardial failure and consisted of morphine as needed,

25. Diggs, L. W.: Personal communication to the authors.

26. Mason, V. R.: Personal communication to the authors.

27. Lawrence, J. H.: Personal communication to the authors.



meralluride, oxygen, lanatoside C and digitalis. The acute phase of myocardial failure subsided. Two days after his admission, his temperature ranged from 99.6 to 102.8 F.; the pulse rate varied from 100 to 140 per minute, and the respirations were 20 to 30 per minute. For this penicillin therapy was added. He was also treated further with liver extract, folic acid, two citrated whole blood transfusions and one transfusion of red blood cells. The course was progressively downward. On the eighth day in the hospital he became disoriented and petechiae appeared over the body. At this time there was tenderness over the splenic area, and the spleen was first palpated. On November 18 a massive gastrointestinal hemorrhage occurred and the patient died, on the fifteenth day in the hospital.

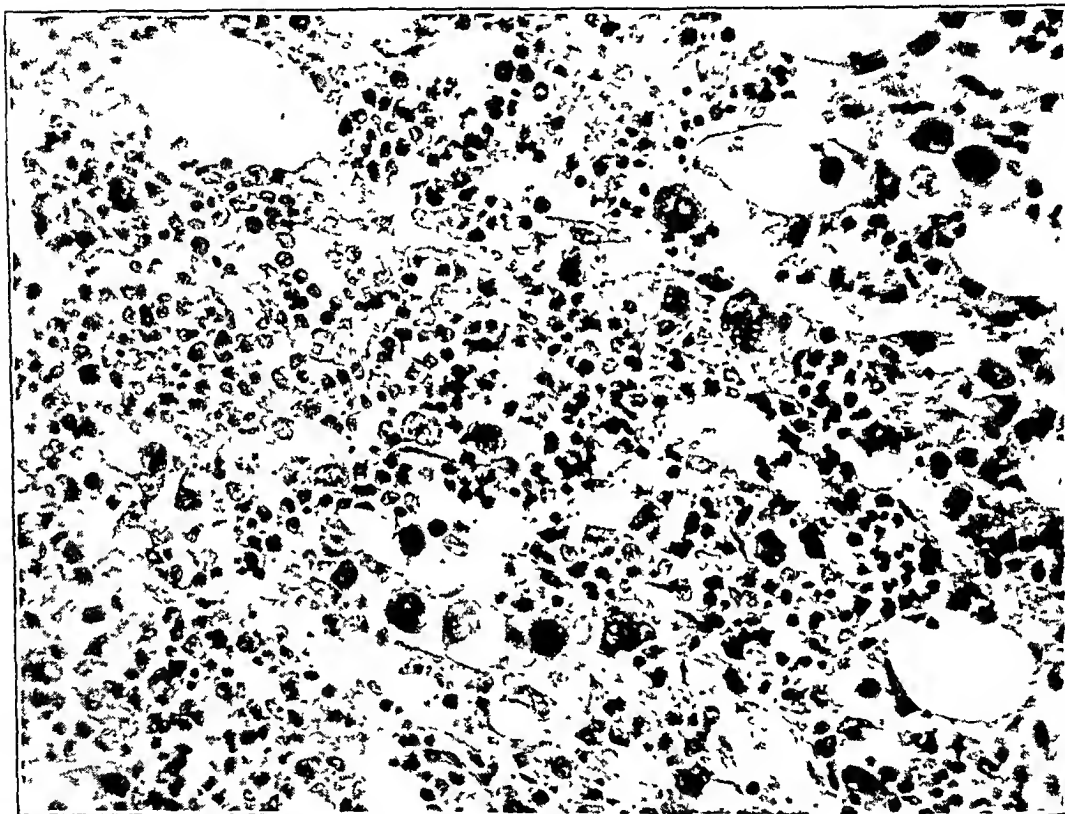


Fig. 6.—Photomicrograph of the vertebrae, showing hyperplasia of all elements, especially the megakaryocytes  $\times 180$ .

*Observations at Necropsy.*—A necropsy was performed four and a half hours after death. The body was that of a well developed, fairly well nourished white man, 66 years of age. The head was of normal contour, and the scalp was covered with thin, receding gray hair. The nares were covered with clotted blood and encrusted herpes. The conjunctiva and buccal mucosa were pale. There was no lymphadenopathy in the neck or in the axillary or inguinal areas. There were numerous petechial hemorrhages over the back and shoulders. The subcutaneous fat was a bright lemon yellow color. There was no free fluid in the peritoneal cavity.

*Thorax:* Each pleural cavity contained approximately 50 cc. of clear, straw-colored fluid. The pericardial sac contained approximately 20 cc. of similar fluid.

**Heart:** The heart weighed 300 Gm. The aortic, pulmonary and tricuspid valve leaflets were essentially normal. The mitral valve was markedly insufficient, and the leaflets were rolled and thickened, with calcification of the entire ring.

**Lungs, Liver and Spleen:** The lungs were similar in appearance. They were mottled grayish pink. In the lower lobe of the left lung there were a few elevated, circumscribed areas, which were of a darker red. The mucosa of the bronchi was slightly hyperemic. The liver weighed 1,690 Gm. It was slightly nodular, and the capsule was smooth. A cut section showed a yellowish brown surface, slightly firmer than normal. The spleen weighed 190 Gm. It was soft, and on section the malpighian corpuscles were prominent.

**Genitourinary System:** The kidneys were similar in appearance. They weighed 130 Gm. each. On section the capsule stripped with a moderate degree of ease, leaving a coarsely granular, mottled grayish and red surface. The cortex was slightly narrowed, the papillae were indistinct and there was an increase in pelvic fat. The ureters and the urinary bladder were normal. The prostate was slightly enlarged and soft.

**Gastrointestinal Tract:** The mucosa of the stomach showed a few petechiae near the pylorus. The mucosa of the duodenum and jejunum was hyperemic. The ileum contained dark red blood clots. Peyer's patches were prominent, and there were hemorrhagic areas scattered throughout the ileum. The lumen of the cecum and remaining portion of the intestinal tract contained dark brownish bloody exudate. There were a few slightly enlarged lymph nodes scattered throughout the mesentery.

Sections of bone marrow from the ribs, sternum and vertebrae were dark red and hyperplastic. The bone marrow from the femur appeared to be composed of a yellow fat.

**Microscopic Study.—Lungs:** There were focal areas of fibrosis. In areas the alveoli contained fibrin and polymorphonuclear leukocytes. Other areas were infiltrated with cells, embryonal in character, and numerous giant cells, megakaryocytic in type. Some of the giant cells were multinucleated, others were in mitoses and in many the nuclei were Y-shaped and atypical.

**Liver (fig. 1):** There was infiltration in the periportal spaces with immature myeloid cells, and giant cells were frequent.

**Spleen (fig. 2):** The architecture of the spleen was distorted. There were islands of extramedullary hematopoiesis. The pulp and sinusoids were filled with immature myeloid cells and giant cells. Macrophages containing a light brown pigment were numerous. There was also similar pigment outside the cells in the connective tissue.

**Kidneys (fig. 3):** In the parenchyma there were focal areas of fibrosis, infiltrated with numerous immature myeloid cells and giant cells.

**Prostate:** This showed an increase in the number of glands with hyperplasia of lining epithelium.

**Gastrointestinal Tract:** There was infiltration in the mucosa with immature blood cells and giant cells. Hemosiderin pigment was also present.

**Mesenteric Lymph Nodes (fig. 4):** The architecture was distorted, and immature blood cells and megakaryocytes were numerous.

**Bone Marrow (figs. 5 and 6):** Sections from the sternum, ribs and vertebrae showed essentially the same picture. There was hyperplasia of all elements, especially of the megakaryocytes, varying from 8 to 15 per low power field. Many were atypical. Mitotic figures were frequent. Sections from the femur showed marrow composed of fat.



*Histologic Diagnosis.*—The histologic diagnosis was acute megakaryocytic leukemia, with leukemic infiltrations and megakaryocytes in the kidneys, liver, spleen, lymph nodes, lungs and intestines and in the bone marrow of the sternum, ribs and vertebrae.

#### COMMENT

The general interest today in leukemia is made evident by the following statistics, taken from the report of Sacks and Seeman.<sup>28</sup> Each year since 1940 more than 5,000 persons in the United States have died of leukemia. Dameshek<sup>29</sup> has expressed the belief that in many instances disorders formerly called anemia and purpura were doubtless leukemia but that these are now being accurately diagnosed. There are probably many atypical cases of leukemia that have been missed or erroneously diagnosed or that have remained unreported because they failed to meet the present criteria set forth in current textbooks. The report given here is a case in point. The patient had a leukemia of unusual type, and after careful consideration of the clinical, hematologic and pathologic studies, it is our belief that this is a true "acute megakaryocytic leukemia." It is apparent that the nosologic system should be revised to include megakaryocytic leukemia as a definite clinical entity.

#### SUMMARY

The salient observations in the case reported were as follows:

In a 66 year old white man who had been observed and studied carefully over a period of years there developed an acute atypical leukemia without apparent splenomegaly or lymphadenopathy. Smears of peripheral blood revealed the presence of aleukemic myeloid leukemia. Aspiration of sternal bone marrow revealed erythromyelomegakaryocytic hyperplasia. No evidence of osteosclerosis or osteofibrosis was present in the roentgenographs or demonstrated at autopsy. Observations at necropsy demonstrated leukemic infiltrations in the viscera. Megakaryocytes were prominent in the lymph nodes, lungs, liver, spleen and kidneys and in the bone marrow of the sternum, ribs and vertebrae.

The paucity of criteria for the diagnosis of megakaryocytic leukemia in the American literature has prompted us to report this case.

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28. Sacks, M. S., and Seeman, I. S.: A Statistical Study of Mortality from Leukemia, *Blood* 2:1-15 (Jan.) 1947.

29. Dameshek, W.: Is Leukemia Increasing? editorial, *Blood* 2:101 (Jan.) 1947.

# Progress in Internal Medicine

## SYPHILIS

A Review of the Recent Literature

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AND

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BALTIMORE

*(Concluded from Page 840)*

### TOXIC REACTIONS TO PENICILLIN

Penicillin has become a valuable adjunct in modern syphilology largely because it is, in comparison to other forms of therapy, relatively nontoxic. Such reactions as do occur have been largely restricted to allergic manifestations and are most often dermal sensitizations. No deaths have been attributed to penicillin therapy, and there have been few serious reactions.

In an experience with more than 5,000 patients treated with penicillin in an army hospital. Mendell and Prose<sup>209</sup> encountered six allergic reactions of such severity that it became necessary to discontinue administration of the drug. Four of these reactions occurred early in the course of therapy, with severe pruritis, erythema and urticaria; two were delayed and simulated serum sickness. Testing for sensitivity to penicillin before administration was found to be neither reliable nor practicable.

An extensive review of the toxic reactions accompanying penicillin therapy has been made by Morginson,<sup>210</sup> who has grouped and discussed reactions to penicillin according to its role as (1) direct toxin and primary irritant, (2) antigen and (3) excitant of therapeutic shock and its indirect action on pathologic processes. Penicillin exerts a negligible action as a direct toxin or primary irritant, except after its intrathecal use. With the latter, reactions (convulsions, meningismus and shocklike state) apparently are due to direct irritative phenomena. There is ample evidence that penicillin possesses antigenic and allergenic properties, although the reactions which result are less frequent with purified preparations. Sensitization attributes of commercial penicillin

209. Mendell, T. H., and Prose, P. H.: Severe Allergic Reactions to Penicillin, *Am. J. M. Sc.* **212**:541 (Nov.) 1946.

210. Morginson, W. J.: Toxic Reaction Accompanying Penicillin Therapy, *J. A. M. A.* **132**:915 (Dec. 14) 1946.

have been demonstrated by positive reactions to patch and intradermal tests, by indirect or passive transfer tests, by precipitin reactions and, in guinea pigs, by Schultz-Dale tests. Sensitivity may be manifested as immediate or delayed reactions. Immediate reactions usually occur in patients who are known to be sensitive to penicillin or who have had previous doses of the drug, although a few persons appear to have a primary sensitivity. Delayed or acquired sensitization may be produced by repeated injections of penicillin and may be of short duration or persist for years. The allergic symptoms following penicillin therapy usually are benign, of low incidence and transient in nature. Therapeutic shock (Jarisch-Herxheimer reaction) incident to the use of penicillin in the therapy of syphilis is frequently encountered. Temporarily intensified local tissue reactions and systemic manifestations occur. An indirect action on pathologic processes in the form of the so-called therapeutic paradox has been postulated.

Fromer<sup>211</sup> classifies the reactions from penicillin used in the treatment of syphilis as: (1) those due directly to penicillin, which are subdivided into (a) early treatment pruritis, i. e., usually a mild generalized itching and dryness of the skin, occasionally with a transient erythema which is not aggravated by continuing penicillin therapy, (b) dermatophytid reactions, occurring in patients with preexisting dermatophytoses and (c) post-treatment urticaria and serum-sickness-like reactions, and (2) Herxheimer reactions, which were observed in approximately 90 per cent of the patients with early syphilis treated.

*Allergic Dermatoses.*—Bauer<sup>212</sup> describes three types of allergic dermatoses complicating penicillin therapy: (1) urticaria, the most frequent reaction, (2) erythematovesicular eruptions, usually occurring within twenty-four hours after penicillin is administered intramuscularly and (3) contact dermatitis from local application. All three reactions are of the acquired type. The degree of individual susceptibility, the degree of contact and the period of exposure are all variable factors which combine to determine the severity of the dermatitis. The mechanism underlying the erythematovesicular reactions to penicillin is considered to be analogous to that producing dermatophytids. Cutaneous tests were of only limited value in the diagnosis of any of the three types of penicillin dermatoses discussed.

Callaway and Barefoot<sup>213</sup> have studied hypersensitivity to sodium penicillin and circulating antibodies by means of intracutaneous, passive

211. Fromer, S.: Reactions in the Treatment of Syphilis with Penicillin, *Arch. Dermat. & Syph.* 55:385 (March) 1947.

212. Bauer, G. H.: Allergic Dermatoses Complicating Penicillin Therapy, *Arch. Dermat. & Syph.* 54:292 (Sept.) 1946.

213. Callaway, J. L., and Barefoot, S. W.: Immunological Studies on Patients Developing Urticaria Associated with Penicillin Therapy, *J. Invest. Dermat.* 7:285 (Dec.) 1946.

transfer and precipitin tests in 5 patients in whom urticaria developed in association with penicillin therapy. Reactions to all intracutaneous and passive transfer tests were negative, and the results of precipitin tests were inconclusive.

Allergic sensitivity reactions were demonstrated by Chu and Cutting<sup>214</sup> in guinea pigs and rabbits with pure crystalline penicillin G and with commercial penicillin. These included mild local urticaria after intradermal injections and lesions characteristic of the Arthus phenomenon. Systemic sensitivity was less notable with the crystalline preparation. It is concluded that the purest obtainable crystalline penicillin can act as a sensitizing agent and that the skin bears the brunt of the allergic reaction.

*The Treatment of Penicillin Urticaria.*—The most frequently encountered reaction to penicillin administered parenterally is urticaria. The experience of Pillsbury, Steiger and Gibson<sup>215</sup> indicates that (1) urticarial reactions are more frequent in patients who have had repeated courses of the drug; (2) some patients in whom urticaria has developed after penicillin therapy may tolerate further use of the drug, whereas others may not; (3) cutaneous tests with penicillin are unreliable as a means of predicting the recurrence of reactions on further administration of penicillin; (4) urticarial reactions may be persistent and severe, and (5) antihistaminic compounds, such as "benadryl hydrochloride" (beta-dimethylaminoethyl benzohydryl ether hydrochloride)<sup>216</sup> and "pyribenzamine hydrochloride" (N' pyridyl-N' benzyl-N-dimethylethylenediamine hydrochloride<sup>217</sup>) are useful in controlling penicillin urticaria.

These authors recommend that when urticarial reactions to penicillin occur injections of the drug be suspended and antihistaminic substances administered by mouth. If the urticaria promptly subsides, a test dose of 1,000 units of another manufacturer's penicillin may be administered, and if no untoward reaction occurs, the dosage should be gradually increased until therapeutic levels are reached. The dosage of antihistaminic substances may gradually be reduced, but if evidences of recurrent sensitivity reactions become evident, "benadryl hydrochloride" or "pyribenzamine hydrochloride" should again be given in full therapeutic doses.

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214. Chu, W. C., and Cutting, W. C.: Allergic Sensitization to Penicillin: Experimental Results, *Proc. Soc. Exper. Biol. & Med.* **63**:347 (Nov.) 1946.

215. Pillsbury, D. M.; Steiger, H. P., and Gibson, T. E.: The Management of Urticaria Due to Penicillin, *J. A. M. A.* **133**:1255 (April 26) 1947.

216. Distributed by Parke, Davis & Company.

217. Distributed by Ciba Pharmaceutical Products, Inc.

An excellent and comprehensive review of the use of newer antihistaminic agents has been made by Feinberg.<sup>218</sup> In the treatment of allergic reactions to the administration of penicillin, favorable reports from the use of "benadryl hydrochloride" recently have been made by Callaway and Barefoot<sup>213</sup> and by Willcox,<sup>219</sup> and beneficial effects from the use of "pyribenzamine hydrochloride" have been observed by Kampmeier<sup>220</sup> and by Feinberg and Friedlander.<sup>221</sup>

*Serum-Sickness-Like Reactions.*—Reactions of the serum sickness type following the parenteral administration of penicillin are well known. Gordon<sup>222</sup> and Eisenstadt<sup>223</sup> again describe this type of reaction. Dressler and Dwork<sup>224</sup> have used procaine hydrochloride by intravenous drip in the treatment of the serum-sickness-like type of reaction to penicillin and report favorable results from it.

*Anaphylactic Shock.*—O'Donovan and Klorfajn<sup>225</sup> report the occurrence of anaphylactic shock following the intramuscular injection of penicillin in a patient who had been sensitized by the use of penicillin spray two months previously.

*Febrile Reactions.*—DeGennes and his co-workers<sup>226</sup> describe, in addition to reactions to penicillin of the erythroderma and the serum-sickness-like type, a febrile reaction which they attribute to the penicillin. In 2 patients high fever persisted despite clinical evidences of disappearance of the acute infection for which the penicillin had been given. When administration of penicillin was discontinued the fever promptly disappeared. The febrile reactions were noted during a period when a new lot of penicillin was being used, and the authors suspect pyrogenic impurities as the cause.

218. Feinberg, S. M.: Histamine and Antihistaminic Agents, J. A. M. A. **132**:702 (Nov. 23) 1946.

219. Willcox, R. R.: Use of "Benadryl" for Penicillin Urticaria, Brit. M. J. **2**:732 (Nov. 16) 1946.

220. Kampmeier, R. H.: The Use of Pyribenzamine Hydrochloride in Controlling Urticaria Due to Penicillin, Am. J. Syph., Gonorr. & Ven. Dis. **31**:57 (Jan.) 1947.

221. Feinberg, S. M., and Friedlander, S.: Histamine Autagonists: IV. Pyridil-N' Benzyl-N-Dimethylethylenediamine (Pyribenzamine) in Symptomatic Treatment of Allergic Manifestations, Am. J. M. Sc. **213**:58 (Jan.) 1947.

222. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, J. A. M. A. **131**:727 (June 29) 1946.

223. Eisenstadt, W. S.: Hypersensitivity to Penicillin Simulating Serum Sickness, Minnesota Med. **29**:689 (July) 1946.

224. Dressler, S., and Dwork, R. E.: Reactions to Penicillin: Procaine Hydrochloride Intravenously in the Treatment of Reactions Similar to Serum Sickness, J. A. M. A. **133**:849 (March 22) 1947.

225. O'Donovan, W. J., and Klorfajn, I.: Sensitivity to Penicillin: Anaphylaxis and Desensitization, Lancet **2**:444 (Sept. 28) 1946.

226. deGennes, L.; Bricaire, H.; Laroche, C., and Nelhil, J.: Les accidents d'intolérance a la pénicilline, Presse méd. **55**:161 (March 8) 1947.

*Exfoliative Dermatitis.*—Nolan and Pedigo<sup>227</sup> report that in a patient who had had urticaria during one course of penicillin exfoliative dermatitis developed when a second course of the drug was given fourteen days after the first had been stopped. They suggest that this reaction was due to some impurity in the penicillin used, since reactions to patch tests were positive with the batch of penicillin that had been administered but not with a different brand of the drug.

*Agranulocytosis.*—Spain and Clark<sup>228</sup> have observed a patient in whom a generalized erythematous macular rash developed, followed by leukopenia and agranulocytosis, during penicillin therapy. There had been other medications (opiates, barbiturates, physostigmine and vitamins K and C); the use of most of these was continued during the agranulocytosis and given afterward without any effect on the white blood cell count. The appearance of the agranulocytosis in association with a cutaneous rash together with a rise in the white blood cell count soon after administration of penicillin was discontinued suggests that the agranulocytosis probably was due to penicillin.

*Purpura.*—Anderson<sup>229</sup> reports on a patient in whom, during therapy with penicillin, purpura developed, there being present the symptoms in the joints described by Schönlein and the intestinal crises described by Henoch. Associated with this was a persistent toxic nephritis.

*Jaundice.*—During recent years, increasing numbers of cases have been reported in which infective hepatitis has been conveyed to patients by means of an infected injection. Hughes<sup>230</sup> reports a series of cases of jaundice following injections of penicillin and considers the condition to have been transmitted from patient to patient by means of contaminated syringes. Evidence is presented to show that a single intramuscular injection of 1 cc. of fluid may lead to contamination of the syringe used.

*Thromboplastic Action.*—The report of Moldavsky, Hasselbrock and Cateno<sup>231</sup> to the effect that penicillin shortens the coagulation time and decreases the bleeding time of normal blood has stimulated others to study the problem.

227. Nolan, D. E., and Pedigo, G. W.: Exfoliative Dermatitis Following Penicillin Therapy, *Ann. Int. Med.* **25**:725 (Oct.) 1946.

228. Spain, D. M., and Clark, T. B.: A Case of Agranulocytosis Occurring During the Course of Penicillin Therapy, *Ann. Int. Med.* **25**:732 (Oct.) 1946.

229. Anderson, A. B.: Anaphylactic Purpura Following Intramuscular Penicillin Therapy, *M. J. Australia* **1**:305 (March 8) 1947.

230. Hughes, R. R.: Post Penicillin Jaundice, *Brit. M. J.* **2**:685 (Nov. 9) 1946.

231. Moldavsky, L. F.; Hasselbrock, W. B., and Cateno, C.: Studies in Mechanisms of Penicillin Action: I. Penicillin Effects on Blood Coagulation, *Science* **102**:38 (July 13) 1945.

Macht<sup>232</sup> expresses the belief that next to its chemotherapeutic properties and low toxicity the most important pharmacologic attribute of penicillin is its thromboplastic activity. The investigator found that amorphous penicillin produced acceleration of the blood-clotting time, an effect that usually persisted for several hours. Comparing various penicillin fractions, he found penicillin X most potent in thromboplastic activity and, in descending order, penicillins K, G, and F to be of lesser potency.

In contrast, Lewis<sup>233</sup> reports that he was unable to demonstrate any in vitro or in vivo effect of penicillin on the coagulation of blood. No significant changes were observed in coagulation time, clot retraction, prothrombin concentration, fibrinogen concentration, platelet count or bleeding time in normal or hemophilic subjects.

Whichever of these two conclusions may be correct, thrombotic accidents in medical practice after the use of penicillin are extremely rare.

*Changes in Viscosity of the Blood.*—Loiseleur, Levy and Sureau<sup>234</sup> report transitory increases in the viscosity of the blood serum during administration of penicillin, which disappear rapidly after the termination of treatment. With amorphous penicillin the change was more striking than with crystalline penicillin. Since the viscosity of the penicillin solutions was less than that of serum itself, it is hypothesized that the increase in viscosity results from the formation of a specific antibody. The authors suggest further that the "antibody" which they have hypothesized may be concerned in some way with the sensitization reactions provoked by penicillin.

*Effects of Penicillin on Menstrual Function.*—McLachlan and Brown<sup>235</sup> report that alterations in the menstrual cycles occurred in 91.3 per cent of 206 women treated with penicillin in varying time-dose schedules. The most frequent changes were lengthening or shortening of the cycle or duration of flow and the occurrence of dysmenorrhea. Uterine cramps and/or bleeding occurred in 43.8 per cent of 32 women who were treated during pregnancy, and in 1 case it was thought that penicillin was responsible for premature induction of labor. Alterations in the lochia were observed in 12 of 16 women treated during puerperium. Lactation was diminished in

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232. Macht, D. I.: Thromboplastic Properties of Penicillin and Streptomycin, *Science* **105**:313 (March 21) 1947.

233. Lewis, J. H.: Effect of Penicillin on Blood Coagulation, *Proc. Soc. Exper. Biol. & Med.* **63**:538 (Dec.) 1946.

234. Loiseleur, J.; Levy, M., and Sureau, B.: Sur les réactions sériques consécutives à l'administration de pénicilline, *Ann. Inst. Pasteur* **72**:931 (Nov.-Dec.) 1946.

235. McLachlan, A. E. W., and Brown, D. D.: Effects of Penicillin Administration on Menstrual and Other Sexual Cycle Functions, *Brit. J. Ven. Dis.* **23**:1 (March) 1947.

75 per cent of this group of patients, and it is recorded that normal lactation usually returned when the use of penicillin was discontinued. The authors express the belief that these effects of administration of penicillin were due to impurities in the drug since there was a decreasing incidence as purer preparations became available.

*Masking of Syphilis by Small Doses of Penicillin.*—Physicians interested in the therapy of gonorrhea have recognized that penicillin administered for gonococcic urethritis may be sufficiently spirocheticidal to alter or mask the symptoms of a concomitantly acquired syphilitic infection. It has been suggested that preclinical syphilis may be recognized by the occurrence of febrile reactions of the Jarisch-Herxheimer type occurring after penicillin therapy for gonorrhea. Fromer, Cutler and Levitan<sup>236</sup> confirm these observations and state the belief that although there are exceptions to the rule it is good practice to subject patients in whom there develops a febrile reaction to penicillin therapy for gonorrhea to close scrutiny, both clinical and serologic, for a period of four months after therapy. Within this period additional evidence of incipient syphilis may well be expected to develop.

That penicillin given routinely for a variety of conditions is likely to obscure the early manifestations of syphilis is again stressed by Cronin,<sup>237</sup> who cites 7 cases in which are illustrated the difficulties in the diagnosis of syphilis caused by penicillin medication for other diseases. This author recommends that before penicillin is administered a complete examination be made and that routine serologic tests be performed. He also suggests that the patient's temperature be taken every three hours for the first twelve hours of administration of penicillin, in the belief that any febrile response suggests a Herxheimer reaction from a subclinical infection with syphilis.

Cronin<sup>238</sup> states that "there is no evidence that penicillin in amounts up to 150,000 units delays the appearance of syphilis for more than 3 months after treatment. Unnecessary psychologic trauma and little benefit will accrue in extending surveillance beyond this period." He bases this conclusion on a survey of the available literature together with an analysis of 19 cases in which syphilis was personally observed to develop after penicillin treatment for gonorrhea.

*Herxheimer Reactions from Penicillin.*—Seeking to avoid the occurrence of Jarisch-Herxheimer reactions by beginning penicillin therapy

236. Fromer, S.; Cutler, J. C., and Levitan, S.: Masking of Early Syphilis by Penicillin Therapy in Gonorrhea, *J. Ven. Dis. Inform.* **27**:174 (July) 1946.

237. Cronin, E.: "Masked" Syphilis: Dangers of Penicillin Therapy, *Lancet* **2**:84 (July 20) 1946.

238. Cronin, E.: The Evolution of Syphilis After Small Doses of Penicillin: A Critical Survey, *Brit. J. Ven. Dis.* **23**:15 (March) 1947.



with small initial doses, Olansky<sup>230</sup> found that even in small doses (1,000 units) the drug evoked in at least 6 patients severe reactions of this type. He concludes that "penicillin, even in small doses, should not be administered to patients with late or complicated syphilis until a course of bismuth has been given."<sup>240</sup>

#### OTHER ANTIBIOTIC PREPARATIONS IN EXPERIMENTAL SYPHILIS

*Streptomycin*.—Fiskin and Gruhitz<sup>241</sup> report that the administration of streptomycin to syphilitic rabbits in doses of 1,000 to 4,000 subtilis units per kilogram of weight per day for a period of twenty days produced no regression of lesions or disappearance of spirochetes. Continued administration of streptomycin to the same rabbits in doses of 6,000, 8,000 and 10,000 subtilis units per kilogram per day for an additional thirteen days did not suffice to heal the overt lesions or achieve cure, since 100 per cent of the animals retained viable organisms as demonstrated by lymph node transfers to other animals. The virulence of the strain of *Treponema pallidum* did not appear to have been altered by the prolonged administration of streptomycin.

Kolmer, Rule and Paul<sup>242</sup> report that streptomycin by intermittent intramuscular injection was slightly but temporarily effective in the treatment of 3 out of 6 rabbits with acute syphilitic orchitis in a total dosage of 24,000 to 240,000 units per kilogram of weight, but complete cures were not observed in any of the animals receiving total dosages of from 24,000 to 240,000 units per kilogram by intramuscular injection over a period of eight days.

*Tyrothricin*.—Kolmer and Rule<sup>243</sup> report that the administration of tyrothricin intravenously to rabbits with acute testicular syphilomas was completely ineffectual. None of 16 animals showed any healing of the testicular lesions, and in no case did dark field examination fail to reveal the persistence of *T. pallidum*.

239. Olansky, S.: The Herxheimer Reactions of Relatively Small Doses of Penicillin, *J. Ven. Dis. Inform.* **28**:26 (Feb.) 1947.

240. It should be remarked that 4 of this author's 6 patients had early syphilis. The only basis for his conclusion is to be found in a consideration of the patient in his case 3, a 32 year old man with gumma of the testis in whom, shortly after the institution of penicillin treatment, there developed fever and a temporary increase in testicular swelling and tenderness.

241. Fiskin, R. A., and Gruhitz, O. M.: The Effect of Streptomycin on Experimental Syphilis Infections of Rabbits, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:581 (Nov.) 1946.

242. Kolmer, J. A.; Rule, A. M., and Paul, A. J.: Streptomycin in Treatment of Acute Syphilitic Orchitis of Rabbits, *Proc. Soc. Exper. Biol. & Med.* **63**:242 (Nov.) 1946.

243. Kolmer, J. A., and Rule, A. M.: Failure of Tyrothricin in the Treatment of Experimental Syphilis of Rabbits, *Proc. Soc. Exper. Biol. & Med.* **63**:375 (Nov.) 1946.

## MALARIA THERAPY

*Quantitative Inoculation with Parasites.*—The febrile course of inoculation vivax malaria, unlike the naturally acquired infection, rarely is one of tertian periodicity. In the majority of cases of induced infections quotidian cycles are exhibited, with varying degrees of irregularity. The administration of 5 to 10 cc. of malarial blood commonly is followed by a period of continuous remittent fever accompanied with malaise and fatigue, often exhausting the patient prior to the establishment of true malarial paroxysms. This initial period of remittent fever has been thought to be the result of asynchronism of different broods of malaria parasites. This asynchronization of parasites following intravenous inoculation apparently is produced by the injection of a large number of organisms in different stages of schizogony, resulting in remittent fever when clinical levels of parasitemia are reached. Synchronization of these broods occurs only after several days of clinical activity has permitted domination by a single brood and cycle.

Kaplan, Read and Becker<sup>244</sup> have sought to eliminate the disturbing period of remittent fever by controlling the technics of inoculation. Intradermal inoculation was followed by the shortest period of, and the least severe, remittent fever. The occurrence of 18.8 per cent of unsuccessful "takes" with this technic, however, makes the routine use of the method unjustified. Intravenous inoculation with doses ranging from 1,000,000 to 150,000,000 parasites revealed in susceptible patients that the higher the dose the longer the period of remittent fever in a high percentage. The lower the dose the shorter and less severe was the remittent fever, resembling the results following intradermal inoculation. It also was possible to correlate the occurrence of the desirable tertian cycle with the technic of inoculation, for the percentage of patients with tertian cycles after intravenous inoculation varied inversely with the parasite dose. The intravenous inoculation of 1,000,000 *Plasmodium vivax* parasites (determined by correlating the amount of inoculum with the quantitative parasite count of the donor) is recommended as a standard procedure in the therapy of neurosyphilis when susceptible white patients are being dealt with. This technic eliminated the period of remittent fever for 35.7 per cent and shortened it to two days or less for 67.9 per cent of patients included in the study.

*Therapeutic Malaria of Foreign Origin.*—Engstrom and his fellow workers<sup>245</sup> inoculated 105 neurosyphilitic patients (172 white and 23

244. Kaplan, L. I.; Read, H. S., and Becker, F. T.: Use of Quantitative Parasite Inoculation Doses in *Plasmodium Vivax* Malaria Therapy, *Arch. Neurol. & Psychiat.* **56**:65 (July) 1946.

245. Engstrom, W. W.; Gordon, H. H., and Marble, A.: Induced Malaria of Foreign Origin, *Arch. Int. Med.* **79**:185 (Feb.) 1947.

Negro) with vivax malaria of Pacific or Mediterranean origin. Their attempts to transfer *P. vivax* malaria, whether by mosquito bites or by inoculation of blood, were highly successful in white patients whether they gave a past history of malaria or not and relatively unsuccessful in Negroes. Spontaneous remission of fever was observed more than three times as frequently in those who gave a history of having had malaria as in those who did not. It was noted that as the disease progressed the concentration of parasites in the blood at first increased rapidly but after the eleventh day began to fall. Sixty-five per cent of the patients inoculated with mosquitoes infected with Pacific strains of *P. vivax* had relapses, whereas no patient relapsed who had been inoculated intravenously with blood containing the same strains. Quartan malaria was transmitted to 48 patients (45 Negro and 3 white) by inoculation of blood containing *Plasmodium malariae*. Quartan infections differed from tertian not only in the longer interval between paroxysms but also in the longer period of incubation, the slower response to quinacrine hydrochloride therapy and the tendency to cause serious renal complications.

*Biochemical Studies During Fever Therapy.*—The biochemical studies of Gall and Steinberg<sup>246</sup> on patients with malarial and artificial fevers revealed the development of transient hypophosphatemia during the febrile paroxysm. In the search for an explanation for the hypophosphatemia, determinations of the blood glucose levels were made at comparable periods. From these studies it became apparent that the fall in serum phosphorus was attended by a rise in glucose in a manner which suggested an inverse relationship between the two. It was thought that the hyperglycemia resulted from an acceleration of metabolism and the simultaneously increased muscular tonus and that the hypophosphatemia was linked with increased utilization of glucose. Hypophosphatemia presumably was associated with the formation and deposition of hexosephosphate in the tissues. No significant alterations were observed in the serum, calcium, potassium, magnesium, creatine or creatinine levels. The serum protein levels fell slightly during malarial fever but remained unchanged in artificial fever.

Pathologic studies in human and experimental malaria have shown lesions not unlike those occurring in shock. It has been suggested that these lesions resulted from anoxemia produced by the rapid destruction of erythrocytes. It is reported by Rigdon and Varnadoe<sup>247</sup> that the administration of oxygen may be beneficial in severe malarial infections.

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246. Gall, E. A., and Steinberg, A.: *Biochemical Studies During Malarial and Artificial Fevers*, J. Lab. & Clin. Med. **32**:508 (May) 1947.

247. Rigdon, R. H., and Varnadoe, N. B.: *Effect of Oxygen on Malaria: An in Vivo Study in Ducks*, J. Lab. & Clin. Med. **32**:57 (Jan.) 1947.

The increased amount of oxygen apparently helped to compensate for the decrease in hemoglobin content. Ducks with a severe malarial infection when placed in an oxygen chamber immediately showed considerable clinical improvement and survived for a longer period than those kept at room temperature. This improvement is attributed to the greater amount of oxygen available for transmission to the anoxemic tissues.

*Tests of Hepatic Function During Therapeutic Malaria.*—Lippincott and his associates<sup>248</sup> have performed tests of hepatic function before, during and after therapy with induced malaria. Although there was evidence of impaired hepatic efficiency in the majority of 138 patients during fever therapy, termination of the therapy resulted in a fairly prompt return to normal, by all indications, of hepatic function. In no case was there any evidence of persistent hepatic damage.

During fever therapy, there occurred in most patients studied retention of sulfobromophthalein, ranging up to 40 per cent. Abnormal values also were observed, during malaria treatment, with the cephalin flocculation test and with the icterus index, serum bilirubin and urobilinogen tests. After the administration of quinacrine hydrochloride, the tendency was for the results in practically all tests to be normal within approximately two months.

Glenn and his co-workers<sup>249</sup> found evidence of impaired hepatic function in all of a group of 60 patients undergoing malarial therapy for neurosyphilis. After termination of the malarial fever, most abnormalities disappeared promptly. The function of detoxification, as measured by the test for hippuric acid excretion, was depressed for the longest period. The degree of hepatomegaly could not be correlated with the severity of hepatic dysfunction. The digestive symptoms experienced during therapeutic malaria appeared not to be due solely to hepatic damage, although anorexia was more frequent as the serum bilirubin level became elevated. The authors could demonstrate no significant protection of the liver by the addition to the diet of protein or vitamins or by injections of crude liver extract. However, the administration of 75 Gm. of dextrose intravenously daily did decrease the incidence of hepatic enlargement.

*Jaundice in Malaria.*—Hills<sup>250</sup> believes that malarial jaundice is a distinct clinical entity characterized by the abrupt onset of painless icterus

248. Lippincott, S. W.; Marble, A.; Ellerbrook, L. D.; Hesselbrock, W. B.; Engstrom, W. W., and Gordon, H. H.: Liver Function Tests in Neurosyphilitic Patients with Induced Vivax Malaria of Pacific and Mediterranean Origin, J. Lab. & Clin. Med. **31**:991 (Sept.) 1946.

249. Glenn, P. M.; Kaplan, L. I.; Read, H. S., and Becker, F. T.: Clinical and Laboratory Studies of Liver Function in Therapeutic Malaria, Am. J. M. Sc. **212**:197 (Aug.) 1946.

250. Hills, A. G.: Malarial Jaundice, Am. J. M. Sc. **212**:45 (July) 1946.

in a patient febrile with malaria. It is of brief duration, averaging seven days in his experience. Enlargement of the liver and bilirubinuria were common. Acholic stools did not occur. Malarial jaundice seemed primarily a hemolytic icterus, but hepatic injury secondary to hemolysis and fever appeared to contribute to the production of the jaundice. There was no evidence that quinine or quinacrine hydrochloride had any part in its pathogenesis.

In this series the forms of disease ranged from minimal hyperbilirubinemia to definite icterus with hemoglobinuria. The author believes that hemoglobinuria is the rule in severe malarial jaundice and that because of its threat to renal function it is a complication to be dreaded. It is concluded that hemoglobinuria will appear in malarial jaundice when hemolysis becomes so intense that the reticuloendothelial system is unable to keep the plasma hemoglobin level below the renal threshold and that the syndrome of blackwater fever may be due solely to unusually severe malarial hemolysis.

Reports such as those of Sartwell<sup>251</sup> and of Ginsburg,<sup>252</sup> both of whom describe cases of homologous serum hepatitis following blood transfusion, raise the possibility that this condition may occur after inoculation malaria. The reviewers have seen several patients in the past few years who became icteric at intervals after inoculation with malarial blood, comparable to the occurrence described by these authors.

*Purpura in Malaria.*—Shrager and Kean<sup>253</sup> report that in 10,000 consecutive patients with malaria treated at Gorgas Hospital there were 10 cases (0.1 per cent) in which the condition was complicated by purpura. Purpura occurred in an untreated patient, but in the other 9 cases the purpura followed the use of quinine. The thrombocytopenic and nonthrombocytopenic varieties of the disease occurred in equal proportion. The complication was a serious one, as 4 of the patients were critically ill, and 2 died.

*Allergy in Malaria.*—Allergic manifestations resulting from the foreign protein in the malarial parasite are medical curiosities. Grazier,<sup>254</sup> who has studied this problem, states that in the few cases described in the literature the allergic phenomena invariably accompanied the onset of fever or appeared immediately preceding it. Allergic manifestations (urticaria) occur at a time when merozoites, being free in the blood stream, make a foreign protein available. The author has observed

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251. Sartwell, P. E.: Infectious Hepatitis in Relation to Blood Transfusion, *Bull. U. S. Army M. Dept.* **7**:90 (Jan.) 1947.

252. Ginsburg, H. S.: Homologous Serum Hepatitis Following Transfusion, *Arch. Int. Med.* **79**:555 (May) 1947.

253. Shrager, J., and Kean, B. H.: Purpura as a Complication of Malaria, *Am. J. M. Sc.* **212**:54 (July) 1946.

254. Grazier, H. F.: Allergy in Malaria, *Ann. Int. Med.* **25**:968 (Dec.) 1946.

approximately 500 cases of malaria, with but 1 instance of specific sensitivity to the malarial parasite, and believes the incidence of allergic phenomena to be even lower than his data suggest.

*Thiobismol in Therapeutic Quartan Malaria.*—The efficacy of “thiobismol” (sodium bismuth thioglycollate) in reducing the frequency of paroxysms of vivax malaria without eliminating them completely is well known. Injections of this drug, by virtue of its inhibitory effect on half-grown *P. vivax* parasites, convert the febrile course from quotidian to tertian periodicity and thus facilitate temporary interruptions of malaria and allow a full course of therapy without rapidly exhausting the patient with daily febrile episodes.

In quartan malaria the use of sodium bismuth thioglycollate is less well understood. Kaplan, Read and Becker<sup>255</sup> report that in 42.5 per cent of 38 patients given “thiobismol” injections there was the desired therapeutic effect. The drug was most frequently effective when administered to patients with double quartan or quotidian quartan malaria. Injections of it resulted in appreciable decreases in the parasite count, the effect being on immature parasites. The authors conclude that “thiobismol is an effective drug for reducing the frequency of paroxysms and regulating the febrile cycles in patients experiencing double quartan or quotidian quartan malaria. Its use may enable patients with neurosyphilis to tolerate better complete courses of therapeutic quartan malaria.”

*Blood Serologic Tests after Malaria Therapy.*—Several common clinical concepts relating to dementia paralytica have been challenged by Kirman.<sup>256</sup> Reviewing the clinical records of 312 patients with dementia paralytica and finding a low incidence (3 per cent) of clinical lesions elsewhere in the body, the author concludes that adjuvant metal chemotherapy is unnecessary after therapeutic malaria. In his experience, moreover, persistently positive serologic reactions following malarial therapy were no more common than in other forms of late syphilis.

#### PROPHYLAXIS OF SYPHILIS

*Mercury.*—Laug and his co-workers,<sup>257</sup> who have studied the absorption of mercury by cutaneous inunction, find the urinary excretion to be an unsatisfactory indication of the degree to which mercury pene-

255. Kaplan, L. I.; Read, H. S., and Becker, F. T.: The Action of Thiobismol on Therapeutic Quartan Malaria, *J. Lab. & Clin. Med.* **31**:735 (July) 1946.

256. Kirman, B. H.: Significance of the Blood Wassermann Reaction After Malaria Therapy in General Paralysis, *Brit. J. Ven. Dis.* **22**:168 (Dec.) 1946.

257. Laug, E. P.; Vos, E. A.; Umberger, E. J., and Kunzi, F. M.: A Method for the Determination of Cutaneous Penetration of Mercury, *J. Pharmacol. & Exper. Therap.* **89**:42 (Jan.) 1947.

trates the skin. They suggest an experimental method dependent on measurements of the quantity of mercury which is stored in the kidney during twenty-four hours of exposure. Using the storage of mercury in the kidney as a measure of the amount that has passed through the skin, they have found that a number of factors influence the cutaneous penetration of mercury: 1. Covering of the site of inunction increased the penetration of mercury fourfold. 2. The location of the site of inunction appeared not to effect the degree of penetration. 3. Removal of excess ointment from the skin reduced the absorption of mercury. 4. Washing of the skin with soap and water before inunction had little or no influence on penetration. 5. After application to smaller areas of skin mercury was less well absorbed than when applied to larger areas.

These same authors<sup>258</sup> report that the cutaneous absorption of mercury is greatly influenced by the vehicle in which it is suspended. In their experience, oleic acid and propylene glycol supported the greatest penetration of mercury. The least satisfactory vehicles appeared to be those most frequently incorporated in prophylactic ointments. Next to the vehicle, the compound of mercury seemed to have the greatest influence on the cutaneous penetration. The concentration of mercury in the prophylactic ointment affected its absorption but slightly, although a twenty-five fold increase in concentration in the ointment caused a doubling of the amount of penetration. Reduction in the particle size of mild mercurous chloride increased the penetration of mercury significantly. The addition of a 15 per cent solution of sulfathiazole to mild mercurous chloride ointment reduced cutaneous penetration by approximately one third. Generally speaking, it appeared that the type of vehicle, whether fat, water-in-oil or oil-in-water emulsion, is less important to penetration of mercury than the constituents which the ointment contains.

*Arsenicals.*—A number of amide-substituted phenylarseneoxides have been shown to be actively spirocheticidal in vitro and to be effective prophylactically in experimental rabbit syphilis when applied as a solution in propylene glycol to an inoculated superficial incision on the skin of the back. Eagle, Magnuson and Fleischman<sup>259</sup> have found that these compounds are less effective prophylactically when incorporated in ointments. There was no significant difference between ointments with a fatty base containing a finely divided arsenical in suspension and ointments with a continuous aqueous phase containing

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258. Laug, E. P.; Vos, E. A.; Kunzi, F. M., and Umberger, E. J.: A Study of Certain Factors Governing the Penetration of Mercury Through the Skin of the Rat and the Rabbit, *J. Pharmacol. & Exper. Therap.* **89**:52 (Jan.) 1947.

259. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Local Chemical Prophylaxis of Experimental Syphilis with Phenyl Arsenoxides Incorporated in Ointments and in Soap, *Am. J. Syph., Gonor. & Ven. Dis.* **31**:257 (May) 1947.

the arsenical in solution. A representative compound (P-arsenosophenoxyacetamide) was active prophylactically when applied as an aqueous solution in dilute soap (5 per cent potassium oleate). The significance of these observations with respect to the prophylaxis of human syphilis is discussed, with particular reference to the possible use of soaps containing stable arsenoxides.

*Penicillin.*—Eagle, Magnuson and Fleischman<sup>260</sup> have shown that the dosage of penicillin necessary to abort syphilitic infections in rabbits when given four days after inoculation increases progressively with the size of the inoculum. After intracutaneous inoculation with 200,000 spirochetes it required fifteen to fifty times as much penicillin to abort the disease as was necessary with an inoculum of only twenty organisms. It was further demonstrated that with a fixed inoculum of 2,000 spirochetes the curative dose of penicillin increased progressively with the duration of the experimental infection. These data suggest to the authors a new approach to the prophylaxis of syphilis, since syphilitic infection in man may perhaps prove susceptible to abortion with relatively small doses of penicillin, provided these are administered promptly.

#### CONTROL OF SYPHILIS

In any process as complex as the control of venereal disease significant changes in one aspect of the program may require alterations in other aspects if the program is to be kept in proper balance.

An obvious need, for example, is the development of some means whereby practicing physicians may be kept informed of newer methods of diagnosis and treatment and of the facilities available for their application. Refresher courses, such as those described by Heyman,<sup>261</sup> offer a possible solution. The physician cooperation plan described by Hollister<sup>262</sup> has as its primary purpose the utilization of private physicians in case finding.

Nonetheless, it should be pointed out that however effective may be the newer therapeutic procedures and to whatever degree cooperation of physicians may be attained effective control of venereal disease also necessitates improved case finding and case holding. Some of the newer technics are outlined in a recent issue of the *Journal of Venereal*

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260. Eagle, H.; Magnuson, H. J., and Fleischman, R.: Relation of the Size of the Inoculum and the Age of the Infection to the Curative Dose of Penicillin in Experimental Syphilis, with Particular Reference to the Feasibility of its Prophylactic Use, *J. Exper. Med.* **85**:423 (April) 1947.

261. Heyman, A.: Postgraduate Instruction in Venereal Disease, *J. Ven. Dis. Inform.* **27**:253 (Oct.) 1946.

262. Hollister, W. G.: Self-Interview Forms in Private Physician Contact-Reporting: A New Technic in Case Finding; a Preliminary Report, *J. Ven. Dis. Inform.* **27**:240 (Oct.) 1946.



*Disease Information.* Bundesen, Bauer and Baker <sup>263</sup> recommend the use of telegrams as an inexpensive and efficacious (in 46.2 per cent. of cases) means of bringing in contacts for examination, at least in urban areas. Koch and Thornton <sup>264</sup> also have found the use of telegrams to be economical and effective in case holding. Rosenthal and Kerchner <sup>265</sup> record that in the New York City Health Department the use of registered letters was successful (20 per cent) in persuading suspected contacts to report for examination.

*Clerical Aspects of Control of Syphilis.*—Without an adequate clerical system, a program for the control of venereal disease, especially that of a local health unit, cannot function properly. Such a program should be planned in terms of smooth clinical function, accurate reporting of morbidity and avoidance of duplication.

A satisfactory clerical system evolved over a period of years is described by Pariser, <sup>266</sup> who divides clerical functions into three phases, i. e., processing, admission and statistics. For the processing of epidemiologic information, two files are considered desirable, which are a central registry and a pending file. The second function, i. e., admission, which is directly concerned with the operation of clinics, requires an "expected in" file, a chart file subdivided into active and inactive categories and a "delinquent file." The third function, dealing with statistical analyses, necessitates the completion of detailed reports on morbidity.

*Control of Syphilis by Quarantine.*—Most local health officers are empowered to quarantine patients with infectious venereal disease in order to prevent further spread of infection, but this power seldom is used. Instead, reliance usually is placed on persuasion and education, with the threat of quarantine reserved for the occasional patient who refuses to cooperate.

During World War II, only one state, South Carolina, used its quarantine powers as a routine, statewide and continuing activity. Chisolm <sup>267</sup> reports on the results achieved in the first year (1945) of its operation. There were prompt and significant increases in the

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263. Bundesen, H. N.; Bauer, T. J., and Baker, A. H.: Evaluative Study of Three Types of Epidemiologic Activity on Three Hundred and Sixty Syphilis Contacts, *J. Ven. Dis. Inform.* **27**:244 (Oct.) 1946.

264. Koch, R. A., and Thornton, M.: Use of Télégrams in Venereal Disease Case Holding, *J. Ven. Dis. Inform.* **27**:246 (Oct.) 1946.

265. Rosenthal, T., and Kerchner, G.: Experiences with Registered Letter Follow-Up in the New York City Health Department, *J. Ven. Dis. Inform.* **27**:249 (Oct.) 1946.

266. Pariser, H.: A Proposed Clerical System for a City Venereal Disease Program, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:181 (March) 1947.

267. Chisolm, J. M.: Control of Syphilis by Quarantine: A State-Wide Quarantine Program for the Control of Infectious Syphilis, *Yale J. Biol. & Med.* **19**:557 (March) 1947.

number of patients with early syphilis admitted to rapid treatment centers and in the percentage with untreated early syphilis sent to hospitals. Improvement in investigation of contacts is claimed. The local health departments experienced little difficulty in enforcing the quarantine, and there was no record of a patient successfully evading quarantine through court procedures.

*Mass Serologic Testing.*—Stimulated by the example of other mass blood-testing programs, the Venereal Disease Control Committee of San Antonio, Texas, decided in the autumn of 1945 to promote a citywide campaign against syphilis. Robbins and Green,<sup>268</sup> who were intimately associated with this program, report that the number of cases of infectious syphilis found as a result of this campaign was "not impressive." They report that when reliance is placed on voluntary mass blood testing promiscuous persons cannot be expected to volunteer for testing in large numbers. The extensive health education accomplished by the program is nonetheless considered to be a noteworthy achievement.

*Investigation of Contacts.*—There has been in recent years an increasing awareness of the importance of efficient case finding in the control of venereal disease. Crowley and Tucker<sup>269</sup> opine that investigation of contacts, if intelligently carried out by competent workers, is one of the most efficacious methods of case finding and one that should take precedence over other technics. In the state of Tennessee the maximum cost of bringing to treatment a single patient with infectious syphilis was \$63.93, a figure lower than any yet recorded for any other method of case finding.

There are no infallible rules to be followed by those who undertake case-finding interviews with patients who have infectious syphilis. Steiger and Taylor<sup>270</sup> outline "some of the points which easily can be overlooked but which have been found useful in contact questioning."

Prerequisites for a successful interview include privacy, an understanding and noncritical attitude on the part of the interviewer, a basic knowledge of the venereal diseases and a knowledge of the patient's individual case. It is suggested that the interview be begun by the establishment of a proper degree of rapport and that much can be accomplished by explaining that the patient's own prognosis has been improved as a result of prompt diagnosis. The authors have been impressed with the results of the "community spirit" approach in obtain-

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268. Robbins, L. C., and Green, W. S.: Preliminary Report on the San Antonio Blood Test Campaign, *J. Ven. Dis. Inform.* **27**:196 (Aug.) 1946.

269. Crowley, E. L., and Tucker, C. B.: The Cost of Venereal Disease Contact Investigation in Tennessee, *J. Ven. Dis. Inform.* **28**:81 (May) 1947.

270. Steiger, H. P., and Taylor, J. B.: Venereal Disease Interviewing, *J. Ven. Dis. Inform.* **28**:55 (April) 1947.

ing the names of sexual contacts. If the name of the contact is unknown to the patient, a detailed description or the circumstances of exposure may suffice for identification. Whether routine or rapid treatment is given, the consideration of case holding is highly important.

*Premarital Serologic Tests for Syphilis.*—In the majority of states of the union premarital serologic tests for syphilis are now required by law. It is generally agreed in support of this type of legislation that it has as its primary objective the control of a considerable proportion of the syphilitic infections which are constantly occurring. This objective is said to be attained by (1) finding patients with syphilis, thus leading to their treatment and the prevention of further spread, (2) preventing the infection of the marital partner, (3) preventing the occurrence of congenital syphilis and (4) educating the public about syphilis. Some of the objections to compulsory premarital serologic testing have recently been summarized by Nelson,<sup>271</sup> who states:

There is no justification for arbitrarily subjecting a part of the general population to blood testing for the purpose of finding cases of syphilis. . . . If mass blood testing is sound, it should be applied to the entire population. . . . Mass blood testing . . . implies that if a person is tested once, the question of his infection with syphilis will be settled for all time. . . . If the *spread* of syphilis is to be prevented by mass blood testing, the infections must be detected *while they are still communicable*. . . . Blood tests would have to be done every few weeks in order to find new infections while they are still communicable. . . . It cost (in Birmingham, Ala.) nearly \$1,000 to find a single openly infectious case by this mass blood testing method. . . .

If the marital partner is to be protected, it must be assumed that the couple do not have intercourse prior to marriage, an assumption which is by no means always valid. It must be assumed, also, that a blood test will determine by itself whether or not a person has syphilis. That cannot be assumed. . . . Those persons who are found to have syphilis in a presumably infectious state, and who are not permitted to marry, will not necessarily discontinue having sexual intercourse. . . .

The only way to prevent congenital syphilis is to *treat the syphilitic mother during pregnancy*. . . . Premarital blood tests do not contribute materially to the prevention of congenital syphilis.

Premarital blood test legislation tends to give legal support to popular misunderstanding of the significance of blood tests, and to perpetuate the notion that the problem of syphilis control can be solved by making blood tests. . . . Premarital blood test laws apply one single and inconclusive test for one single disease condition to the whole question of fitness to marry. This is poor premarital public education. . . .

In a provocative article Leider<sup>272</sup> ponders certain theoretic considerations in the planning of venereal disease control. Pointing out

271. Nelson, N. A.: Why Is a Pre-Marital Blood Test Law Unsound Legislation? *Baltimore Health News* **24**:127 (May) 1947.

272. Leider, M.: Theoretical Considerations in Venereal Disease Control Planning, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:325 (May) 1947.

that the spread of the genitoinfectious diseases implies sexual promiscuity, he suggests that disregard for the sexual and moral adjuncts has led to errors or deficiencies in the control of venereal disease, which should be approached more as control of behavior. In this writer's opinion, "the control of venereal diseases is a social problem primarily, with incidental medical and moral aspects." Continent or strictly monogamous sexual habits are not considered to be ends impossible of attainment. If such social behavior had been characteristic of the members of the armed forces during the last war, "a great deal of lubricious fun would have been missed to be sure, but so would several million new cases of venereal disease, unnumbered illegitimacies, much juvenile and adult delinquency and a heritage and tradition of martial grossness."

#### SYPHILIS AND OTHER DISEASES

*Yaws.*—It is generally believed that in yaws late manifestations of the disease are comparatively rare. Osseous lesions, such as gangosa (rhinopharyngitis mutilans) and goundou (exostoses of the nasal and frontal bones), are now considered to be tertiary manifestations of yaws, but involvement of the cardiovascular and central nervous systems is almost unknown.

Smith,<sup>273</sup> while stationed in the Marshall Islands during World War II, was impressed by the ataxia of many of the native stevedores who had had long-standing infection with yaws. He could demonstrate none of the neurologic abnormalities of tabes dorsalis other than ataxia, but in 1 case there were changes in the joints in one knee and one ankle that were compatible with the Charcot type of arthropathy.

Padilha Goncalves<sup>274</sup> reports that it is occasionally possible to produce the lesions of pinta in patients with acute or latent yaws by experimental inoculation with *T. carateum*. Among 9 patients with yaws there were 2 in whom lesions of pinta developed. The fact that inoculations were unsuccessful in 7 is adduced as evidence of a partial immunity conferred by yaws against pinta.

*Cancer.*—Laitinen,<sup>275</sup> after analyzing 2,073 cases of cancer at the University Hospital in Helsinki, concludes that "syphilis has comparatively frequently an influence in the origin of cancer, but it is by no means one of the principal causes of it. Syphilis gives origin to cancer by means of prolonged irritation caused by local changes." In his

273. Smith, F. H.: Charcot-Like Joints in Yaws, U. S. Nav. M. Bull. **46**: 1832 (Dec.) 1946.

274. Padilla Goncalves, A.: Sobre la transmision de pinta experimental a frambesicos, Bol. Soc. cubana de dermat. y sif. **3**:169 (Dec.) 1946.

275. Laitinen, H.: Ueber die Korrelation zwischen Syphilis und Krebs, Duodecim **34**:111, 1945.

material the incidence of syphilis in patients "at cancer age" in Finland was 1 to 2 per cent. Among the 2,073 patients with cancer the incidence of syphilis was 6.6 per cent. Concomitant syphilitic infection was most frequently present in patients with cancer of the female genital organs, lungs, anus and rectum, mouth and tongue. A higher incidence of syphilis was not apparent among patients with squamous cell carcinoma of the skin, cancer of the central portion of the digestive tract or cancer of the upper respiratory tract. Cancerous lesions developing in patients with syphilis progressed in a manner similar to those developing in nonsyphilitic persons, and there was no demonstrable difference between the two groups in their response to radiation therapy.

*Genital Tuberculosis.*—On rare occasions a primary tuberculous complex may occur on the skin or mucous membranes. There may then be a tuberculous ulcer, with involvement of the regional lymphatic channels and nodes. As Bjørnstad's <sup>276</sup> 2 cases illustrate, such tuberculous lesions may occur on the genitalia as a result of infection in venery. The diagnosis is established by histopathologic and bacteriologic examination of tissue after syphilis, lymphogranuloma venereum and chancroidal infection have been excluded. When, as in the 2 cases here reported, the sexual partner is known to have urogenital tuberculosis, the diagnosis is more readily apparent. Patients with tuberculosis of the genitourinary tract should be informed of the danger of contagion, particularly for sexual partners with negative reactions to the tuberculin test.

Sonck <sup>277</sup> describes a case in which a middle-aged man who had had tuberculous pleurisy, cervical lymphadenopathy and apparently benign pulmonary involvement (but no signs of involvement of the urinary tract) had, over a period of ten years, recurrent papulonecrotic tuberculids of the penis. The genital lesions were accompanied with recurrent keratoconjunctivitis, often appearing simultaneously with recurrences of the penile lesions.

The subject of tuberculosis of the penis has recently been reviewed by Lewis, <sup>278</sup> who records that the lesion may be either primary or secondary to pulmonary or genitourinary foci. Of 110 cases previously reported, in 72 the condition was the result of ritual circumcision. The lesion most frequently starts as a papule, which usually ulcerates. Because of its appearance, its clean base and the presence of induration,

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276. Bjørnstad, R.: Tuberculous Primary Infection of Genitalia: Two Cases of Venereal Genital Tuberculosis, *Acta dermat.-venereol.* **27**:106, 1946.

277. Sonck, C. D.: A Case of Papulo-Necrotic Tuberculides on the Penis, *Acta dermat.-venereol.* **27**:45 (June) 1946.

278. Lewis, E. L.: Tuberculosis of the Penis: A Report of Five New Cases, and a Complete Review of the Literature, *J. Urol.* **56**:737 (Dec.) 1946.

tuberculosis of the penis readily is confused with primary syphilis. Treatment usually is unsatisfactory, and the prognosis is unfavorable.

*Behcet's Syndrome.*—To be differentiated from syphilis and other genitoinfectious diseases is the triple symptom complex which has come to be known as "Behcet's syndrome." This condition, named for the Turkish dermatologist who in 1937<sup>279</sup> first integrated its several manifestations, is characterized by aphthous-like ulcerations of the oral and genital mucous membranes and a variety of ocular disturbances, the most characteristic of which is uveitis with hypopyon. Apparently, it encompasses the conditions which have been known as "ulcus vulvae acutum" and "periadenitis mucosa necrotica recurrens" and is to be distinguished from aphthous stomatitis, pemphigus and erythema multiforme.

The reported cases have involved young adults of either sex, who appear otherwise to be in good health. The genital and oral lesions, which usually appear first, are recurrent and resistant to treatment. Ocular involvement, though protean in its manifestations, usually is first manifested as an iritis or uveitis, with subsequent hypopyon and blindness.

The cause of Behcet's syndrome is not known, although it is probably of virus origin. *Bacillus crassus*, which is considered by some to be identical with Döderlein's bacillus and which has been found only in the genital lesions, appears to be either a secondary invader or, more probably, a nonpathogenic saprophyte. There is as yet no consistently efficacious therapy.

Katzenellenbogen,<sup>280</sup> who reports 3 cases in which the three symptoms were present, notes that in his patients the lesions on the oral mucosa had a predilection for the lower lip, that lesions on the genitalia consisted of sharp-edged ulcers with preference for the scrotum and that although the mucosal ulcerations healed after local therapy the ocular manifestations were resistant to all forms of treatment and led to blindness. Other lesions noted were erythema-nodosum-like nodules on the extremities, acneform eruptions and recurrent epididymitis. All 3 patients had unusual dermal sensitivity. Pustules formed at the site of puncture of the skin, and injection of any of a number of different substances was followed by erythema. Cowpox vaccination is suggested as a therapeutic procedure, presumably on the basis of possible virus antagonism.

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279. Behcet, H.: Ueber rezidivierende, aphthöse, durch ein Virus verursachte Geschwülste im Mund, am Auge und an den Genitalien, *Dermat. Wchnschr.* **105**: 1152 (Sept. 4) 1937.

280. Katzenellenbogen, I.: Recurrent Aphthous Ulceration of Oral Mucous Membrane and Genitals Associated with Recurrent Hypopyon Iritis (Behcet's Syndrome): Report of Three Cases, *Brit. J. Dermat.* **58**:161 (July-Aug.) 1946.

Curth's review<sup>281</sup> of "recurrent genito-oral aphthosis and uveitis with hypopyon" is the first in the American literature and the most complete thus far available. This author reports 2 additional cases in which bacteriologic studies yielded no clue as to the cause and in which various therapeutic measures (vitamin therapy, removal of foci of infection, vaccination, oral administration of sulfonamide drugs and injection of penicillin) were ineffectual.

Prosser Thomas' case report<sup>282</sup> is unique in that there was an associated thrombophlebitis and in that pathologic study of an excised eye is reported. There was complete detachment of the retina, with gross intraocular hemorrhage, chiefly subretinal. Marked patchy thickenings of the ciliary body and the choroid were evident, but there was no evidence that vascular thrombosis was the initial factor. O'Donnell<sup>283</sup> reports the association of Behcet's syndrome with epididymitis, geographic tongue and gastric symptoms.

*Condylomata Acuminata*.—In 1942 Kaplan<sup>284</sup> introduced a simple and effective method of treatment for condylomata acuminata, consisting of topical application of a 25 per cent solution of podophyllin in mineral oil.

Anderson<sup>285</sup> testifies to the efficacy of this treatment. Finding it difficult to keep the podophyllin suspension confined to the lesions, this author modified the method by using a 10 per cent tincture of resin of podophyllin applied with a cotton swab. The surrounding normal skin may be protected by an ointment consisting of 5 per cent aluminum powder in zinc oxide paste.

Sullivan and King<sup>286</sup> have treated 50 patients by a slight modification of Kaplan's method and have achieved rapid and spectacular clinical cures in 48, or 96 per cent. Within a few hours after treatment, signs of involution are manifested by shrinking, pallor and loss of moisture. In twenty-four to forty-eight hours the verrucous masses decrease rapidly in size, and they disappear within three to six days, with little or no residual scarring. Irritation of the adjacent mucous membranes occurs

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281. Curth, H. L.: Recurrent Genito-Oral Aphthosis and Uveitis with Hypopyon (Behcet's Syndrome): Report of Two Cases, *Arch. Dermat. & Syph.* **54**: 179 (Aug.) 1946.

282. Prosser Thomas, E. W.: So-Called Triple-Symptom Complex of Behcet, *Brit. M. J.* **1**:14 (Jan. 4) 1947.

283. O'Donnell, J. M.: Behcet's Triple Syndrome, *M. J. Australia* **1**:730 (June 14) 1947.

284. Kaplan, I. W.: *Condylomata Acuminata*, New Orleans M. & S. J. **94**: 388 (Feb.) 1942.

285. Anderson, C. R.: Treatment of Condyloma Acuminatum with Resin of Podophyllin, *Arch. Dermat. & Syph.* **54**:66 (July) 1946.

286. Sullivan, M., and King, L.: Treatment of Condylomata Acuminata with Podophyllin, *Bull. U. S. Army M. Dept.* **6**:200 (Aug.) 1946.

in most cases, but this subsides promptly. Patients should be cautioned lest the podophyllin suspension be transferred by the fingers to the eyes.

Studying the mode of action of podophyllin, King and Sullivan<sup>287</sup> found that its application to normal skin produces unusual changes in the epidermis. There are alterations in nuclear pattern, with break-up of chromatin masses and production of pyknotic fragments as well as cytoplasmic changes consisting of swelling, shrinkage from the cell membrane, hydrops, delicate fibrillation and alterations of staining reactions. Histologic examination of condylomas in the process of involution following applications of podophyllin showed numerous such "podophyllin cells."

Suspensions of colchicine in oil, applied in a similar manner, appeared superior to podophyllin in the treatment of condylomata acuminata. Neither was effective when applied to verrucae vulgares or other lesions with extensive keratinization, which suggests that the penetrating power of the drugs is slight. The mode of action of locally applied podophyllin and colchicine seems to be similar. There is a direct, immediate degenerative action, with resultant death of cells.

Finkle and Frishwasser<sup>288</sup> warn that severe balanitis may complicate the use of podophyllin for condylomata acuminata. They recommend that when 25 per cent podophyllin in mineral oil is used it should be removed from contact with the skin and mucous membranes within five hours.

*Other Genital Lesions.*—That ulcerative lesions of the genital mucous membranes may be caused by *Micrococcus tetragenus* has been shown by Pinck and Zhentlin.<sup>289</sup> Because of the low virulence of this organism, infection ordinarily occurs subsequent to a predisposing disease which reduces the resistance of the host.

Herpes progenitalis is seldom recognized in women, though actually it is not uncommon. Slavin and Gavett<sup>290</sup> report 3 cases of vulvovaginitis due to herpes virus in which the diagnosis was proved by isolation of the virus and demonstration of a rising titer of circulating antibodies. The clinical picture was distinctive. Superficial erosions involved considerable areas of the labia minora, adjacent labia majora and vaginal mucous membranes. The ulcers were tender and were usually covered

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287. King, L. S., and Sullivan, M.: The Similarity of the Effect of Podophyllin and Colchicine and Their Use in the Treatment of Condylomata Acuminata, *Science* **104**:244 (Sept. 13) 1946.

288. Finkle, T. H., and Frishwasser, E. J.: Treatment of Penile Condylomata Acuminata with Podophyllin, *J. Invest. Dermat.* **8**:199 (April) 1947.

289. Pinck, B. D., and Zhentlin, B.: Penile Ulcer Caused by *Micrococcus Tetragenus*, *Bull. Johns Hopkins Hosp.* **80**:198 (April) 1947.

290. Slavin, H. B., and Gavett, E.: Primary Herpetic Vulvovaginitis, *Proc. Soc. Exper. Biol. & Med.* **63**:343 (Nov.) 1946.



by a grayish yellow membrane. Some of the lesions appeared to have been autoinoculated.

*Circumcision and Venereal Diseases.*—Wilson,<sup>291</sup> who has reviewed the records of 1,000 consecutive cases at a Canadian Army Venereal Disease Treatment Center, reports that the incidence of all venereal diseases was significantly higher among uncircumcised males than among those who had been circumcised. Ninety per cent of all his cases of primary syphilis and 73.5 per cent of his cases of gonorrhea involved uncircumcised persons. There were 22 cases of balanitis and 18 cases of venereal warts, all in the uncircumcised group.

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291. Wilson, R. A.: Circumcision and Venereal Disease, *Canad. M. A. J.* 56:54 (Jan.) 1947.

## Correspondence

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### IMMERSION HYPOTHERMIA

*To the Editor:*—In the January 1947 number of the ARCHIVES is published an article by Major Edgar Wayburn, entitled "Immersion Hypothermia." In it a citation is made which I believe should not pass without comment. I refer to the discussion, on page 90, of the results claimed by Germans who experimented on their prisoners in concentration camps. It is now generally known that such experiments were done and that the most horrible crimes in this respect were committed. It has been a matter of discussion in some quarters whether the results obtained in such a way should be discarded or eventually made use of. My personal opinion is that nothing can be gained by suppressing really valuable scientific knowledge because it has been acquired in a criminal way. The suffering of the victims cannot be alleviated by our refusing to acknowledge the scientific data which their misery may have yielded. I am firmly convinced, however, that the data acquired by human experiments in German concentration camps are in general without any scientific value whatever. I cannot judge the results cited by Dr. Wayburn in his paper, for I was not a direct witness to these or other human experiments. On the other hand, a nearly two year stay as prisoner in the medical service of the concentration camp at Buchenwald has given me some knowledge of the value of scientific data gained in these circumstances. Often experiments were supervised by non-medical, unsufficiently trained personnel. But, what is more important, the men who had to compile the data were, and could not be, primarily concerned with their exactness. Their first interest was to give their SS guards the results they were looking for. It may be difficult for those who have never known life as a prisoner in a German concentration camp, or even in German-occupied territory, to understand to how few primitive principles life may be reduced. But, certainly, objective, unbiased scientific experimentation and gathering of data for the SS were not among them.

The scientific value of the "extraordinary series of experiments" cited by Dr. Wayburn therefore seems doubtful. Besides, I do not think that experiments such as these should be cited without once more drawing attention to their unpardonable nature. Furthermore, the perpetrators of these crimes should not be mentioned among decent scientists in a list of authors, as has been done here. Neither should they be alluded to as German investigators. Let us not forget that men the like of these are now being tried for crimes against humanity.

Human life and health are, or at least should be, still too valuable to experiment on. This will be accorded by every one in the face of

the aforementioned experiments. I believe it should also be seriously considered by those who, as seems to be a growing custom, experiment with human volunteers.

R. J. HAMBURGER, M.D., Netherlands.

Alkmaar Holland, Wilhelminalaan 8.

*To the Editor:*—My sympathy goes out to Dr. R. J. Hamburger and any other human being unfortunate enough to be confined in a German concentration camp. I have no objection to the publication of his letter about the article "Immersion Hypothermia," published in the January 1947 issue of the ARCHIVES.

As he says, "Nothing can be gained by suppressing . . . scientific knowledge because it has been acquired in a criminal way." I did not comment on the reliability of the data obtained by the German investigators (investigators they were for good or evil) except to remark that certain data agreed with my own findings. I see no further need to comment now.

490 Post Street.

EDGAR WAYBURN, M.D., San Francisco.

# News and Comment

## GENERAL NEWS

**Third Interamerican Cardiological Congress.**—The Interamerican Society of Cardiology has authorized the meeting of the Third Interamerican Cardiological Congress to be held in Chicago, at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the annual meeting of the American Heart Association, June 18 and 19, and the Annual Session of the American Medical Association, the week of June 20. Inquiries regarding the congress may be addressed to the offices of the Third Interamerican Cardiological Congress, Michael Reese Hospital, Chicago.

## SOCIETY NEWS

**Brazilian Society of Cardiology.**—The fourth annual meeting of the Brazilian Society of Cardiology was held in São Salvador da Bahia the week of July 1 to 7, 1947. The main subject of the meeting was hypertensive heart disease and rheumatic heart disease.

The 1948 meeting of the society will be held in Porto Alegre. The subjects to be discussed are rheumatic heart disease and social assistance of the patient with cardiac disease.

The following officers have been elected for the current year: Prof. Otavio Magalhães, president; Dr. Aldo Chaves, vice president; Prof. Roberto Menezes de Oliveira, general secretary; Prof. Horacio Kneese de Mello, second secretary; Dr. Emiliano Lourenço Gomes, treasurer, and Prof. Jairo Ramos, director of the *Arquivos*.

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## CORRECTION

In the article by Dr. Clifford H. Peters and his associates entitled "Neurologic Manifestations of Infectious Mononucleosis, with Special Reference to the Guillain-Barré Syndrome" in the September issue (ARCH. INT. MED. 80:366, 1947) the number "9,700" in the fifth line of the fifth paragraph of the "Report of Cases" on page 367 should read "97," and the number "36,000" in the seventh line of the second new paragraph on page 368 beginning "On September 24," should read "36."

## Book Reviews

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**Quantitative Clinical Chemistry: Interpretations.** By John P. Peters, M.D., and Donald D. Van Slyke, Ph.D., Sc.D. Second edition. Volume 1. Price, \$7. Pp. 1,050, with 62 illustrations. Baltimore: Williams & Wilkins Company, 1946.

The first volume, "Interpretations," of the new edition of Peters and Van Slyke's book deals with four topics. Part I covers the subject of energy metabolism. Slightly more space is devoted to this subject in the new edition than in the previous one. Many of the tables contained in the first edition have been omitted. Articles written as recently as 1945 are mentioned, and the presentation of most topics in this section has been revised. A few minor subjects are presented, as in the first edition. Some new topics have been added; these include a discussion of the estimation of metabolism from perspiration.

Part II is concerned with carbohydrate metabolism. This section is much larger than that in the previous edition and has been subdivided into chapters dealing with chemistry and physiology and with clinical application of existing knowledge concerning carbohydrate metabolism. This section represents a comprehensive treatment of the subject, including recent advances in knowledge concerning the mechanism of carbohydrate degradation in the body.

The section on lipids represents a vast improvement over that in the preceding edition. The literature has been covered thoroughly, and most experimental observations on the subject are recorded. Included under the topic of lipids are chapters on steroid hormones and fat-soluble vitamins. One might question the wisdom of publishing as an accepted fact the structural formula of a steroid nucleus attached to vitamin C when the only supporting reference given is to the unpublished work of one author.

The fourth part of the book deals with the various aspects of protein metabolism. Some of the experiments with isotopes which give an insight into the dynamics of protein metabolism are included in this section.

In general the style of presentation of the subject matter is much the same in this as in the previous edition. Medical students who have complained bitterly in the past when referred to this book will find no less cause for lamentation in the future. However, those who seek access to an exhaustive résumé of studies made in a given field will be saved much time and effort by consulting this work before looking elsewhere. It is a great satisfaction to the investigator to know that there is available in the English language such a reliable and comprehensive treatment of these subjects. It is hoped that the new edition will prove to be more substantially bound than its predecessor.

**The Nature of Disease up to Date: An Outline of a Unitary Theory.** By J. E. R. McDonagh, F. R. C. S. Price, 15s. net. Pp. 168. London: William Heinemann, Ltd.; New York: Grune & Stratton, Inc., 1946.

According to "Who's Who," 1946, the author of this monograph is a British medical consultant who, at the same time, is engaged in medical research. The statement appears in this usually reliable source of information that his investigations have resulted in the discovery of the cause of syphilis and of the common cold

and influenza and in the introduction of several preventive and combative remedies for use in the various manifestations of disease. He has literary attainments as well, having published several books, and, above all, an ambition to correlate all diseases, whatever their nature, in relation to his interpretation of their physico-chemical process.

The present volume is a continuation of three others which also deal with the nature of disease. The same two criticisms are pertinent of the third member of the series as the *Lancet* (1021 [Nov. 15] 1924) noted of the first: It is remarkably tedious to read, and in parts it is impossible to understand. Nor can American readers be encouraged to embark on it without being reminded of an earlier comment, still valid, which the *Lancet* expressed to prospective readers when the first volume was reviewed, namely, that the author uses his imagination too frequently and too freely.

**Eye Manifestations of Internal Diseases.** By I. S. Tassman, M.D. Second edition. Price, \$10. Pp. 614, with 243 illustrations, 24 in color. St. Louis: C. V. Mosby Company, 1946.

The appearance of a second edition of this book in a relatively short time after the first edition was published indicates that the book has been exceptionally well received. The favorable reception is well merited.

The second edition has been enlarged by the addition of a description of a number of new diseases and an enlargement on the treatment of various conditions. Just how valuable the latter addition will be is questionable. After all, the book is primarily a publication on the ocular expressions of internal disease, and the treatment of internal diseases should be left to the internist in the great majority of cases.

The reviewer would much prefer to see the space allotted to many unusual and rare diseases and their treatment, also more reproductions of eyegrounds. The internist is primarily interested in the eyegrounds, which are probably the most frequently examined by him in conjunction with a study of the eye. He is rarely interested in local disorders of the eye, which have a distant or questionable relation to internal medicine.

**Narco-Analysis: A New Technique in Short-Cut Psychotherapy, A Comparison with Other Methods and Notes on the Barbiturates.** By J. Stephen Horsley. Price, \$2.50, 8s. 6d. Pp. 134. London: Oxford University Press, 1943; New York: Oxford University Press, 1944.

This brief monograph is a succinct outline of "a new technique in short-cut psychotherapy." The method, which the author began to use in 1931 and perfected in the urgency of modern war, consists in the induction of hypnosis in a patient already narcotized with barbiturates, so that he reveals hitherto repressed, emotionally traumatic experiences and becomes accessible to the physician's therapeutic suggestions. A further, deep narcosis may be added by the injection of additional barbiturates to secure a restful sleep of twelve or more hours.

The author is a pioneer in the field, and his method, variously modified by many others, has proved to be one of the popular, if not unfailingly successful, psychiatric procedures evolved during the war. His exposition in this little volume is lucid and instructive. He nevertheless makes it clear that the personal influence of the physician on the patient is of greater importance than any mere technic. The book can be recommended as an excellent introduction and the appended bibliography as a guide to the physician in his wider pursuit of the subject.

**Lehrbuch der Urologie.** By J. Minder, M.D. Price, 37.50 Swiss fr. Pp. 348. Bern, Switzerland: Buchhandlung und Verlag Hans Huber, 1946. Distributor in United States, Grune & Stratton, Inc., New York.

This is a concise and complete textbook on urology. The reviewer was especially impressed with the marginal paragraph headings which make it simple to find a particular paragraph or subhead when using the book as a reference. The illustrations are not as numerous or in many instances as good as in most American textbooks, although the diagrams are clear and easily understandable. The book follows a logical sequence and is an excellent textbook for any medical student who can read German fluently.

The reviewer was also particularly impressed with the small amount of importance and stress which is laid on the subject of transurethral resection and also with the relative unimportance with which hormonal therapy and castration in the treatment of carcinoma of the prostate is handled. Apparently in the eyes of Professor Minder these two subjects have not reached the same degree of popularity or importance as they have in this country.

This is a good reference text for both the urologist and the general practitioner.

**Textbook of Medical Treatment.** Edited by D. M. Dunlop, L. S. P. Davidson, and J. W. McNee. Fourth edition. Price, \$8. Pp. 944, with 38 illustrations. Baltimore: Williams & Wilkins Company, 1946.

This is a notably popular book, requiring new editions almost every other year. It made its appearance in 1939. The *New England Journal of Medicine* (223:43 [July] 1940) was among the first to recognize it as an outstanding text. Reviews of earlier editions in *The Journal of the American Medical Association* and in the ARCHIVES OF INTERNAL MEDICINE were also complimentary.

The second edition appeared in 1942 and the third in 1944, and now the fourth is at hand. This is much like its predecessors but is brought up to date by careful editing and occasional new chapters.

As the ARCHIVES (75:144 [Feb.] 1945) has stated, the volume presents an excellent and conservative statement of modern treatment in internal medicine. It is especially interesting as showing the almost complete harmony now evident in British and American therapeutic practice.

The latest edition promises to maintain for the book the prominent position which it has attained in former printings. One can safely prophesy its continued success.

**Office Endocrinology.** By Robert B. Greenblatt, M.D. Third edition. Price, \$4.75. Pp. 320, with 71 illustrations. Springfield, Ill.: Charles C Thomas, 1947.

This book contains a great deal of useful information. It is in no sense a systematic or comprehensive textbook of endocrinology. The major portion consists of brief chapters dealing with certain problems which confront the physician, especially in female endocrinology, for example the chapters with the following headings: "The Mechanism of Uterine Bleeding," "Dysmenorrhoea," "Hormonal Therapy of Fibromyomas of the Uterus," "Acne in Adolescence," and "Endocrine Headaches." There are chapters on "Hormonology," in which the availability and use of specific preparations are dealt with. There are numerous excellent illustrations. The book should be useful to the general practitioner, although in a subject of this sort not all will agree entirely on the best method of procedure.

# ARCHIVES of INTERNAL MEDICINE

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## RENAL ARTERIOVENOUS ANASTOMOSES IN RABBITS, DOGS AND HUMAN SUBJECTS

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LOS ANGELES

ALTHOUGH arteriovenous anastomoses had previously been described in various organs by some of the older anatomists, little attention was focused on them until Grant and Bland<sup>1</sup> demonstrated direct connections between the arterioles and veins in the rabbit's ear and in human skin. These shunts are believed to be physiologically important in the control of the flow of blood through the skin and in the regulation of body temperature.<sup>2</sup> The existence of arteriovenous anastomoses in the normal human heart was recently shown in our laboratory by a technic involving the injection of glass spheres of known sizes into the coronary arteries.<sup>3</sup> It was decided to employ the method of injection of glass spheres in a search for such anastomoses in the normal human kidney in view of the lack of agreement concerning their existence in this organ and the potential physiologic significance of renal arteriovenous shunts.

The literature on this subject to 1939 has been thoroughly reviewed by Clara.<sup>4</sup> There are three views regarding arteriovenous anastomoses

From The Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

1. Grant, R. T.: Observations on Direct Communications Between Arteries and Veins in the Rabbit's Ear, *Heart* **15**:281, 1930. Grant, R. T., and Bland, E. F.: Observations on Arteriovenous Anastomoses in Human Skin and in the Bird's Foot with Special Reference to the Reaction to Cold, *Heart* **15**:385, 1931.

2. Clark, E. R.: Arteriovenous Anastomoses, *Physiol. Rev.* **18**:229, 1938.

3. Prinzmetal, M.; Simkin, B.; Bergman, H. C., and Kruger, H. E.: Studies on the Coronary Circulation: II. The Collateral Circulation of the Normal Human Heart by Coronary Perfusion with Radioactive Erythrocytes and Glass Spheres, *Am. Heart J.* **33**:420, 1947.

4. Clara, M.: *Die arterio-venösen Anastomosen*, Leipzig, Johann Ambrosius Barth, 1939.



in the normal human kidney: (1) Several investigators<sup>5</sup> have demonstrated arteriovenous anastomoses in the kidney by injection into the renal arteries of substances such as gelatin, dyes, silver nitrate and celloidin. Steinach<sup>5c</sup> injected Lycopodium spores (average diameter 29 to 32 microns) into the renal artery and recovered some from the renal vein. (2) Some workers have observed arteriovenous anastomoses only in the renal capsule.<sup>6</sup> (3) Other investigators,<sup>7</sup> employing similar technics, were unable to demonstrate arteriovenous channels in either the kidney or its capsule. More recently, Loomis and Jett-Jackson<sup>8</sup> failed to find a single example of arteriovenous anastomoses in their dissections of over a hundred kidneys, and Oliver<sup>9</sup> indicated that these anastomoses may exist, but probably not frequently. Shonyo and Mann<sup>10</sup> were unable to demonstrate any arteriovenous anastomoses in neoprene casts of normal kidneys in several animal species, although they did observe direct shunts between artery and vein in the boundary zone of two hypertrophied rat kidneys.

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5. (a) Gross, C. F.: *Essai sur la structure microscopique du rein*, Inaug. Dissert., Strassbourg, Truettel & Wurtz, 1868. (b) Sucquet, J. P.: *Recherches sur le rein: D'une circulation du sang spécial au rein des animaux vertébrés mammifères et de la sécrétion des urines qu'elle y produit*, Paris, A. Delahaye, 1877; *Commentaire sur la structure microscopique du rein des vertébrés. A l'occasion d'un mémoire de M. Ch.-F. Gros sur le même sujet*, *ibid.* 1869. (c) Steinach, E.: *Studien über den Blutkreislauf der Niere*, *Sitzungsber. d. k. Akad. d. Wissensch. Math.-naturw. Cl.* (pt. 3) **90**:171, 1884. (d) Golubew, W. Z.: *Ueber die Blutgefässe in der Niere der Säugetiere und des Menschen*, *Internat. Monatschr. f. Anat. u. Physiol.* **10**:541, 1893. (e) Dehoff, E.: *Die arteriellen Zuflüsse des Kapillarsystem in der Nierenrinde des Menschen*, *Virchows Arch. f. path. Anat.* **228**:134, 1920. (f) Spanner, R.: *Der Abkürzungskreislauf der menschlichen Niere: Beitrag zur Kenntnis der Leistungszweitelung ihres Gefässsystems*, *Klin. Wchnschr.* **16**:1421, 1937.

6. Golubew:<sup>5d</sup> Geberg, A.: *Ueber directe Anastomosen zwischen Artereen und Venen in der Nierenkapsel*, *Internat. Monatschr. f. Anat. u. Histol.* **2**:223, 1885.

7. Vastarini-Cresi, G., cited by Clara.<sup>4</sup> Langley, J. N.: *The Course of the Blood of the Renal Artery*, *J. Physiol.* **60**:411, 1925. Hou-Jensen, H. M.: *Die Verästelung der Arteria renalis in der Niere des Menschen*, *Ztschr. f. d. ges. Anat.* **91**:1, 1929. von Möllendorff, W.: *Der Exkretionsapparat*, in *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1930, vol. 7, p. 1. Huber, G. C.: *The Arteriolae Rectae of the Mammalian Kidney*, *Am. J. Anat.* **6**:391, 1907.

8. Loomis, D., and Jett-Jackson, C. E.: *Plastic Studies in Abnormal Renal Architecture: VI. An Investigation of the Circulation in Infarcts of the Kidney*, *Arch. Path.* **33**:735 (June) 1942.

9. Oliver, J.: Personal communication to the authors.

10. Shonyo, E. S., and Mann, F. C.: *An Experimental Investigation of Renal Circulation*, *Arch. Path.* **38**:287 (Nov.) 1944.

In the American literature and standard textbooks of anatomy and histology, scant attention has been given to the occurrence of these channels in the normal kidney. In recent reviews of the renal circulation<sup>11</sup> the general opinion has been that if such vascular channels do exist in the normal human kidney, they are exceedingly rare.

It is the purpose of this study to investigate this problem by a method which allows the quantitative measurement of the largest vascular channels connecting the arterial and venous sides of the renal circulation. Previous studies employed postmortem materials, hence it will also be the purpose of this study to determine whether or not functional arteriovenous anastomoses exist in the kidneys of rabbits and dogs during life.

#### I. DEMONSTRATION OF ARTERIOVENOUS ANASTOMOSES IN NORMAL HUMAN KIDNEYS WITH INTACT CAPSULES, POST MORTEM

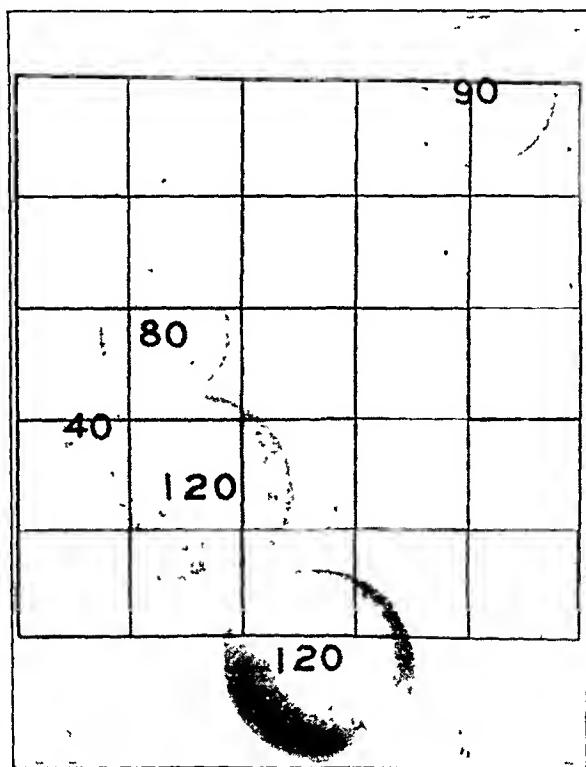
*Principle of Method.*—Glass spheres,<sup>12</sup> suspended in a radiopaque mixture, were injected into the renal artery and recovered from the renal vein. The diameters of the spheres so recovered indicate the size of the lumens of the largest vascular channels permitting the passage of the beads from the arterial to the venous side of the renal circulatory tree. The recovery from the renal vein of spheres with diameters many times greater than the average diameter of a capillary (8 microns) would indicate the presence of arteriovenous shunts.

*Method.*—Human kidneys were obtained at necropsy one to twenty-four hours after death. The kidneys were obtained from patients ranging from 1 to 72 years of age. The renal artery and the renal vein were cut close to the aorta and the inferior vena cava, and the kidney was removed from its bed intact. In most instances the perirenal fascia and fat were left adherent to the removed specimen. In all cases the renal capsule was intact. Some of the kidneys were kept at 4 C. (39.2 F.) twelve to twenty-four hours before being used, and others were used immediately following autopsy. This time factor had no influence on the experimental results. The renal artery and the vein were cannulated with glass cannulas of appropriate sizes; when more than one renal artery or vein were present, they were also cannulated.

11. Smith, H. W.: *The Physiology of the Kidney*, New York, Oxford University Press, 1937. Collins, D. A.: Hypertension from Constriction of Arteries of Denervated Kidneys, *Am. J. Physiol.* **116**:616, 1936. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A. S.: Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption and Diuresis: Mechanism of Urea Excretion, *ibid.* **109**:336, 1934. Walker, A. M.; Schmidt, C. F.; Elsom, K. A., and Johnston, C. G.: Renal Blood Flow of Unanesthetized Rabbits and Dogs in Diuresis and Antidiuresis, *ibid.* **188**:95, 1937.

12. Glass spheres were obtained from Prismo Products, 1211 Architect's Building, Los Angeles.

The injection mixture used in these experiments consisted of 2 Gm. of glass spheres<sup>13</sup> suspended in 100 cc. of a gelatin radiopaque mass.<sup>14</sup> This suspension of beads, warmed to a temperature of 40 C. (104 F.) so that the mass became fluid, was injected into the renal artery by means of a 50 cc. Luer syringe attached to the cannula with a piece of rubber tubing. Just prior to the injection of the glass spheres, 50 to 100 cc. of Ringer's solution at 40 C. (104 F.) was perfused through the renal artery. The perfusing pressure was intermittent, was usually 50 to 100 mm. of mercury and never exceeded 160 mm. of mercury. After 10 to 15 cc. of the suspension had been injected into the renal artery, the radiopaque mass issued from the renal vein and was collected in a test tube. In every instance that the radiopaque mixture was obtained at the renal vein, glass beads were recovered from the perfusate.



Glass spheres as seen under the microscope, with reticule superimposed. Each square of reticule is 80 microns under low power magnification. The number superimposed on the sphere is the diameter of the sphere expressed in microns ( $\times 100$ ).

In order to isolate the glass spheres contained in the radiopaque perfusate, the lead and mercury salts had to be dissolved. The following procedure was used: Concentrated potassium hydroxide was added to dissolve the lead carbonate; the supernatant fluid was carefully decanted, and the sediment was washed with distilled water three or four times. Small amounts, approximately 1 cc. each, of concentrated hydrochloric acid and nitric acid were added, and after gentle heating

13. One gram of beads was estimated to contain approximately 6,000,000 spheres.

14. Prinzmetal, M.; Kayland, S.; Margoles, C., and Tragerman, L. J.: A Quantitative Method for Determining Collateral Coronary Circulation: Preliminary Report on Normal Human Hearts, *J. Mt. Sinai Hosp.* 8:933, 1942.

the mercury sulfide dissolved. The beads were again washed several times with distilled water. Since the glass spheres were heavier than the washing fluids, they settled to the bottom of the test tube, and several minutes were allowed for settling after each washing. The beads at the bottom of the tube were transferred to a glass slide with the aid of a rubber policeman, and their diameters were determined by microscopic examination, with the aid of a calibrated reticule in the eye piece (figure). It should be mentioned that the glass spheres were observed to be impervious to the chemical action of the strong acids and alkalis necessary to clear the opaque mixture.

A roentgenogram of the perfused kidney, made to determine the degree of filling of the renal vessels, showed that the vascular tree was completely filled.

In these studies, kidneys were considered normal in the absence of any arterial or arteriolar disease, as determined by gross and microscopic examination. Kidneys with other types of gross abnormality, such as hypertrophy, atrophy, hydronephrosis and diffuse inflammatory processes, were not included in the series of normal kidneys. Such common observations as acute passive congestion and cloudy swelling were not considered as pathologic in these experiments.

*Results.*—Glass spheres were injected into the renal arteries of sixteen different normal human kidneys with intact capsules, and glass spheres were recovered from the renal vein in every instance (table 1). In these sixteen kidneys the largest spheres recovered ranged in size from 90 to 440 microns in diameter, and in ten of the sixteen kidneys the maximum diameters of the recovered spheres were 200 microns or more. No variation with age was apparent. In the few diseased kidneys examined (table 1) there was no difference in the size of the recovered spheres as compared with the normal kidneys.

These observations indicate the existence of direct arteriovenous communications which must by-pass the capillary bed in the normal human kidney, since the spheres recovered from the renal vein were far too large to have passed through capillaries. It must be emphasized that these arteriovenous shunts were demonstrated in every kidney receiving injections, but the experiments did not indicate whether the by-passing channels were present in the renal capsule and/or in the kidney substance proper.

## II. DEMONSTRATION OF ARTERIOVENOUS SHUNTS IN THE NORMAL DECAPSULATED HUMAN KIDNEY POST MORTEM

In the preceding experiment it was shown that arteriovenous communications were present in kidneys with intact capsules. Since arteriovenous anastomoses have been described in the renal capsule,<sup>6</sup> it was possible that these capsular vessels alone could have accounted for the spheres recovered from the renal vein. Furthermore, in the preceding experiment gross observation showed that vessels in the capsule and perirenal fascia were filled with the radiopaque mass. In order to determine whether arteriovenous anastomoses were present in the body of the kidney, these experiments were repeated in a series of decapsulated normal human kidneys.

*Method.*—The kidneys were obtained, prepared and glass spheres injected in the same manner as described in the preceding experiment, except that they were stripped of their capsules prior to the injection of the spheres. Remnants of the capsule were tied off by ligatures at the hilus. In early experiments it was observed that there were many leaks from the surface of the decapsulated kidney, since some cortical blood vessels entering the capsule were torn when the capsule was stripped. The injection mixture flowed freely from the leakage sites at the

TABLE 1.—*Human Kidneys with Intact Capsules Post Mortem*

No.	Age	Sex	Cause of Death	State of Kidney	Diameter of Largest Sphere Recovered from Renal Vein (Microns)
1	1	M	Tuberculous meningitis	Normal	340
2	38	M	Generalized peritonitis	Normal	180
3	42	F	Subacute portal cirrhosis	Normal	140
4	46	F	Carcinoma of liver	Normal	390
5	53	F	Carcinoma of breast with generalized metastases	Normal	390
6	54	M	Myocardial infarction	Normal	200
7	54	M	Bronchopneumonia	Normal	220
8	57	F	Rheumatic heart disease with congestive failure	Normal	360
9	58	M	Myocardial infarction	Normal	440
10	61	M	Bronebogenic carcinoma	Normal	410
11	65	F	Chronic ulcerative colitis with perforation of sigmoid	Normal	410
12	66	F	Myocardial infarction	Normal	180
13	71	F	Carcinoma of head of pancreas with metastases	Normal	170
14	72	F	Perforation of transverse colon	Normal	390
15			(Data not available)	Normal	110
16			(Data not available)	Normal	90
17	63	F	Cerebral thrombosis	Nephrosclerosis, minimal	180
18	66	F	Cerebral hemorrhage	Nephrosclerosis, minimal	380
19	70	F	Myocardial infarction	Nephrosclerosis, moderate	210
20	35	F	Subacute bacterial endocarditis	Renal infarct	190
21	52	M	Acute hepatitis	Cholemic nephrosis	370
22	70	M	Ruptured arteriosclerotic aneurysm of abdominal aorta	Hydronephrosis	170
23	83	M	Myocardial infarction	Cortical cysts, bilateral	180

surface. Under these conditions, the radiopaque fluid always appeared at the renal by roentgenograms of these kidneys.

A plaster of paris cast was formed around each of the decapsulated kidneys, in order to prevent the diversion of the injected mixture through leaks on the renal surface. Under these conditions, the radiopaque fluid always appeared at the renal vein following injection into the artery, just as in experiment 1.

*Results.*—Glass spheres were injected into the renal arteries of seven different normal decapsulated kidneys obtained from patients ranging from 46 to 75 years of age, and in every instance glass spheres

were recovered from the renal vein. The maximum diameters of the recovered spheres ranged from 100 to 200 microns (table 2).

The results indicate the existence of arteriovenous shunts in the body of the decapsulated kidney.

### III. DEMONSTRATION OF ARTERIOVENOUS ANASTOMOSES IN THE KIDNEYS OF LIVING ANESTHETIZED RABBITS AND DOGS

Although the existence of arteriovenous anastomoses in the normal human kidney post mortem was clearly demonstrated in the aforementioned experiments, the important question as to whether or not these communications exist in life remained unanswered. In order

TABLE 2.—*Postmortem Observations in Human Decapsulated Kidneys*

No.	Age	Sex	Cause of Death	State of Kidney	Diameter of Largest Sphere Recovered from Renal Vein (Microns)
1	46	F	Cor pulmonale	Normal	100
2	49	M	Carcinoma of stomach with perforation	Normal	200
3	53	F	Carcinoma of breast with generalized metastases	Normal	110
4	58	M	Myocardial infarction	Normal	100
5	63	F	Portal cirrhosis	Normal	170
6	64	F	Multiple myeloma	Normal	140
7	75	F	Myocardial infarction	Normal	110
8	65	M	Congestive failure due to hypertensive arterio-sclerotic cardiac disease	Benign nephro-sclerosis	330
9	83	F	Cerebral thrombosis	Benign nephro-sclerosis	190
10	83	M	Myocardial infarction	Cortical cysts, bilateral	340

to determine this point, glass spheres were injected into the renal arteries of living anesthetized animals.

*Method.*—Experiments were performed on 14 healthy adult male rabbits. With the animal under ether anesthesia the left renal artery was exposed through the abdomen, because of greater ease of exposure and manipulation. The adrenal gland on the same side was tied off, since part of its blood supply is derived from the renal artery. In 7 rabbits the renal capsule was intact, and in 7 animals the capsule was stripped. Glass beads suspended in a mixture of a saline solution and rabbit erythrocytes were injected into the renal artery with an "asepto" syringe through an 18 gage needle.

Technical difficulties, such as hemorrhage and cannulation of veins, precluded the recovery of spheres directly from the renal vein, and, therefore, some other way of recovering them from the venous circuit was necessary. In previous studies,<sup>3</sup> it was observed that the lungs trapped practically all of the beads injected intravenously into living rabbits, and the lungs, therefore, were used as a trap for beads which entered the venous circulation. Since beads were injected into the renal artery, any beads recovered from the lungs had to pass through the kidney

and enter the venous circulation. The heart and lungs were removed two to five minutes after the injection into the renal artery. These tissues were completely digested by hot concentrated potassium hydroxide, and the glass beads were recovered after several washings with water.

Inasmuch as the renal artery of a rabbit is small and the 18 gage needle used for injection completely fills the lumen of the artery, the flow of blood into the kidney is momentarily halted, resulting in renal ischemia. Because this unphysiologic factor could not be prevented in an animal as small as the rabbit, with the method of study used, animals with renal arteries of larger caliber were studied. For this reason injections were made into the renal arteries of 2 dogs in exactly the same manner as already outlined. In the dog, the renal flow of blood was not appreciably impaired by the insertion of the needle into the renal artery. The renal capsule was intact in 1 dog; in the other the kidney was decapsulated.

*Results.*—Following the injection of glass spheres into the renal arteries of the 14 rabbits and 2 dogs, the spheres were recovered from

TABLE 3.—*Diameters of Spheres Recovered from Lungs of Rabbits and Dogs*

No. of Animal	Diameter of Largest Sphere Recovered from Lungs (Microns)
Rabbit 1.....	100
Rabbit 2.....	90
Rabbit 3.....	110
Rabbit 4.....	160
Rabbit 5.....	160
Rabbit 6.....	100
Rabbit 7.....	150
Rabbit 8.....	170
Rabbit 9.....	80
Rabbit 10.....	50
Rabbit 11.....	140
Rabbit 12.....	170
Rabbit 13.....	180
Rabbit 14.....	160
Dog 1.....	140
Dog 2.....	80

the lungs in every instance (table 3). In the series of 7 rabbits (rabbits 1 through 7) with the renal capsules intact, the largest spheres recovered varied in size from 90 to 160 microns, and in the rabbits with decapsulated kidneys (rabbits 8 through 14) spheres with diameters ranging from 50 to 180 microns were recovered from the lungs. The perfused kidneys were always packed with beads of all sizes up to 440 microns in diameter, indicating that the injected spheres entered the kidney. No quantitative determination was made of the percentage of injected beads which reached the lungs.

The results in the experiments with dogs confirmed the observations in the experiments with rabbits. In the dog with the intact renal capsule (dog 1), the largest sphere recovered from the lungs measured 140 microns; in the dog with the decapsulated kidney (dog 2), the largest sphere recovered from the lungs was 80 microns in diameter.

The observations in these experiments indicate the existence of arteriovenous shunts in the kidneys of living rabbits and dogs.

#### COMMENT

According to the classic concept of the renal circulation first worked out by Bowman,<sup>15</sup> all of the arterial blood passes through the glomerular capillaries, and then via the efferent arterioles it enters a second capillary bed, the peritubular capillaries. This idea of the renal vascular system has served, up to the present time, as the basis of all physiologic studies of the flow of blood through the normal kidney. However, various vascular channels that by-pass glomeruli have been described in the literature. Shonyo and Mann<sup>10</sup> have listed these by-passing vessels as follows: (1) a direct continuation of the interlobular artery into capillaries of the cortex, (2) Ludwig's arteriole, that is, a branch from an afferent arteriole in the boundary zone which passes directly into the medullary capillaries, (3) arteriae rectae verae, that is, branches from the arcuate arteries or the bases of the interlobular arteries which pass directly into capillaries in the medulla, and (4) direct arteriovenous shunts between the larger vessels.

The present investigation has demonstrated the existence of those vascular channels which by-pass all of the capillary beds in the kidney of the rabbit, the dog and human subjects. These channels must represent direct arteriovenous shunts. The present studies offer no information concerning the other short-circuiting vessels which terminate in capillaries. No exact anatomic localization of arteriovenous anastomoses in the kidney was attempted, except for showing that these shunts were present in the decapsulated kidney and therefore were present in the body of the kidney proper.

Since the spheres which passed through the arteriovenous shunts were recovered from the lungs, it is obvious that many of the larger spheres must have settled all along the way from the renal vein to the lung via the inferior vena cava and the right side of the heart. In fact, in the one experiment, when the inferior vena cava was examined for spheres, larger beads were seen in this location than in the lung. Therefore, it is probable that even larger spheres than recorded on the basis of experimental procedure must have traversed the arteriovenous communications.

The method of study employed in this investigation cannot be used to determine the number of arteriovenous communications in the kidney. A mathematical formula has previously been devised<sup>3</sup> which theoretically should have enabled us to determine the number

15. Bowman, W.: On the Structure and Use of the Malpighian Bodies of the Kidney with Observations on the Circulation Through that Gland, Phil. Tr., London 132:57, 1842.



of communicating channels of different diameters in any organ. However, since large beads settle out faster than small ones, this formula could not be applied. In the light of this factor of settling of the large spheres, it should be emphasized again that the actual diameters of the arteriovenous shunts are probably greater than indicated by the observations in the experiments with animals.

The demonstration of arteriovenous anastomoses in living rabbits and dogs affirms the validity of the postmortem observations in human subjects. Furthermore, the experiments with animals indicate that these anastomoses are patent and functioning during life. It is suggested that if glass beads can pass through these channels, blood may also flow through them. The functional significance of the renal arteriovenous shunts is not known, but on teleologic grounds they probably serve some useful function, since they have been demonstrated during life. It may be that their function is analogous to that of the glomic bodies in the digits, and they therefore may serve as a factor in the regulation and control of renal flow of blood. The demonstration of these shunts during life further contributes to the concept of an extraglomerular or accessory circulation in the normal kidney. Although there has been an accumulation of evidence delineating the anatomic components of an extraglomerular circulation, little is known about the percentage of renal flow of blood that is directed through the extraglomerular circulation under normal and pathologic conditions. If the concept of a functional extraglomerular circulation in the normal kidney is accepted, a reevaluation of the dynamics of renal flow of blood is in order. For example, clearance tests must be reconsidered in this light, with the possibility in mind that rather than measure total renal flow of blood, one measures that proportion of blood which goes to the renal tubules. This may be a variable fraction of the total renal flow of blood. Alterations of renal hemodynamics in reflex anurias, shock and other pathologic states may be intimately concerned with the role of an accessory renal circulation.

Recently, a beginning in these directions has been made by Trueta and his associates<sup>16</sup> in preliminary reports. They have demonstrated a physiologically active accessory medullary circulation in certain circumstances. In their studies on rabbits they observed that "as a result of appropriate nerve-stimulation the blood may be diverted

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16. Trueta, J.; Barclay, A. E.; Franklin, K. J.; Daniel, P., and Prichard, M. M. L.: Renal Pathology in the Light of Recent Neurovascular Studies, *Lancet* **2**:237, 1946. The Lesser Circulation of the Kidney, editorial, *ibid.* **2**:239, 1946. Barclay, A. E.; Daniel, P.; Franklin, K. J.; Prichard, M. M. L., and Trueta, J.: Records and Findings Obtained During Studies of the Renal Circulation in the Rabbit with Special Reference to Vascular Short-Circuiting and Functional Cortical Ischemia, *J. Physiol.* **105**:27P, 1946.

wholly or partly from the cortex and short-circuited through medullary (especially subcortical) blood channels." Their histologic observations suggested the vasa recta and their loops in addition to a subcortical plexus of vessels as the by-passing channels involved. The arteriovenous shunts may serve as the pathways for the rerouting of the renal flow of blood described in Trueta's experiments, although it is admitted that the blood could just as easily be diverted through medullary capillaries. At any rate, it is conceivable that a few arteriovenous communications could account for the passage of a great deal of blood.

At the present time, arteriovenous anastomoses have been described in many tissues and organs. In his classic monograph, Clara<sup>4</sup> listed the following sites where arteriovenous anastomoses have been observed: nose, ear, glomus coccygeum, ovaries, submandibular salivary gland, kidney, stomach, small intestine, mesentery, lymph nodes and brain. In our laboratory these shunts have been demonstrated in the human heart and kidney. All of this evidence suggests a universal distribution of arteriovenous anastomoses and a fundamental, but as yet poorly understood, role in the local regulation and control of the circulation.

#### SUMMARY AND CONCLUSIONS

Glass spheres of known size were injected into the renal arteries of normal human kidneys post mortem, and the existence of arteriovenous anastomoses was indicated by recovery from the renal vein of spheres with diameters many times greater than the average diameter of a capillary. The recovered spheres measured 90 to 440 microns in diameter. These large spheres were recovered from the renal veins of kidneys with and without intact capsules, showing that arteriovenous anastomoses were present in the body of the decapsulated kidney.

The existence of renal arteriovenous anastomoses during life was demonstrated by injection of glass spheres into renal arteries of living anesthetized rabbits and dogs and the recovery of spheres measuring 50 to 180 microns in diameter from the venous circulation. These observations were obtained in animals with and without intact renal capsules.

Since it was observed that renal arteriovenous anastomoses were present and patent in vivo, it is suggested that they function and have physiologic significance during life.

## THROMBOSIS AS A COMPLICATION OF INTERNAL DISEASES

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IN FORMER years it has chiefly been surgeons who have spoken of thrombotic complications. In the medical services thrombosis and thrombophlebitis have more often been considered as independent illnesses and have as a rule been treated by strict confinement of the patient to bed for a long period.

Recently, however, observations have led to the conclusion that thrombosis can occur as a complication of a number of internal diseases in cases other than those in which old age and long confinement to bed have predisposed to its occurrence. It may develop in cases of pneumonia and bronchopneumonia, cardiac disease and anemia.

The danger of the occurrence of thrombosis in pneumonia is illustrated by the following case.

In a man 55 years of age pneumonia developed five days before he was admitted to the hospital. He was given sulfadiazine therapy, but his temperature remained at about 100.4 F. (chart 1A). No signs of continuing pneumonia were present, nor could any reason for the fever be detected. After he had been in the hospital two weeks pulmonary embolism developed suddenly, which resulted in death. The autopsy revealed thrombi in the vessels of the lower part of both legs and large embolic masses in the pulmonary arteries.

Apart from the rise in temperature there was in this case no symptom which suggested the presence of thrombosis.

In cases of pneumonia the temperature frequently does not return to normal. The cause varies. In a number of cases a severe pleuritic effusion is in the process of development and can cause the rise in temperature, but in a not inconsiderable number a thrombosis, usually localized in the venous system of the pelvis or of the lower extremities, has developed. Small pulmonary emboli from this source accompanied with a small quantity of blood-streaked sputum are extremely common in the course of pneumonia. It has even been considered that blood-streaked sputum is part of the symptomatology of pneumonia, especially when the amount of sputum increases. It has been supposed that mechanical strain on the vessels, due to the cough, has caused rupture. This is true only in exceptional cases, since this blood-streaked sputum is found even when the cough has been quelled by narcotics. In my

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opinion small pulmonary embolisms are the cause; pointing to the existence of a thrombosis which should immediately receive specific therapy. The appearance of blood-streaked sputum is therefore an important symptom which suggests the presence of a thrombosis giving rise to emboli. Such a thrombosis can often be difficult of diagnosis. As in the case mentioned, a large thrombosis can occur without subjective symptoms, and even objective signs can be lacking in the course of a routine examination. This is especially true when the thrombus is localized in the pelvic veins.

My colleagues and I have therefore given anticoagulants in all cases of pneumonia in which the temperature has not returned to normal after

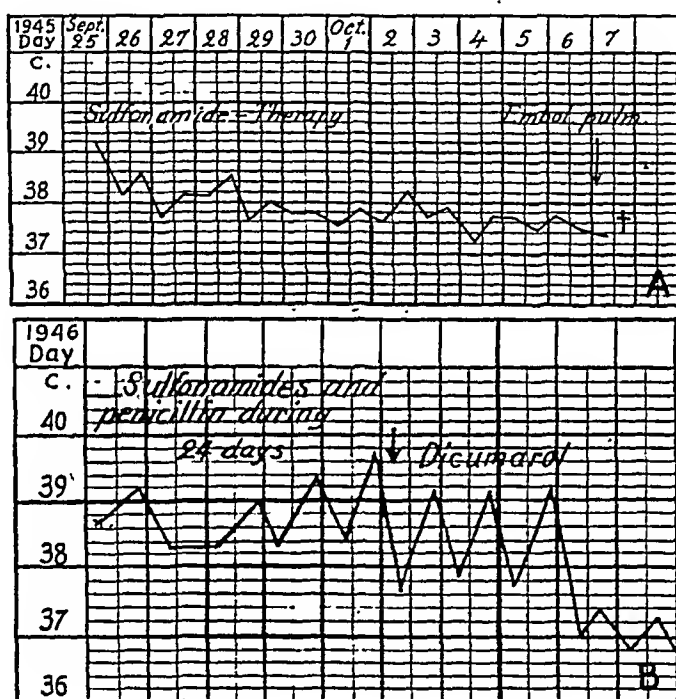


Fig. 1.—A, temperature of a patient with bilateral bronchopneumonia treated with sulfonamide compounds; B, effect of "dicumarol" on the temperature of a patient with bronchopneumonia.

therapy with sulfonamide drugs or penicillin, and in which there has been no reason to suspect the development of an effusion or the presence of some septic complication. The results have been remarkable, as can be seen from the following cases.

A 40 year old man (chart 1 B) suffered from severe ulcerative colitis. Colostomy was performed. Bilateral bronchopneumonia developed postoperatively, and sulfonamide compounds and penicillin were given. The general condition was poor. Despite chemotherapy the temperature varied between 38 C. (100.4 F.) and 40 C. (104 F.) for twenty-four days. "Dicumarol" was then administered, and within three days the patient was afebrile.

A 66 year old woman (chart 2 A) who had previously been treated for hypertension and cardiac insufficiency was admitted to the hospital suffering from bilateral

bronchopneumonia. She was treated with sulfadiazine and penicillin for six weeks, without any improvement. "Dicumarol" was then administered, and the temperature went down rapidly, the pulmonary symptoms regressed and the patient became afebrile and was discharged from the hospital free from symptoms after one and a half weeks.

A 62 year old man (chart 2 B) contracted bronchopneumonia and was treated with sulfadiazine. After six days of chemotherapy the temperature was still between 38 C. (100.4 F.) and 39 C. (102.2 F.). "Dicumarol" was administered, and after three days he was free from symptoms.

In many cases in which the pneumonia is resistant to sulfonamide compounds or penicillin a complicating deep thrombosis is the cause. Therapy with heparin or "dicumarol" has given rapid results in such cases. The temperature has usually become normal after three to four days. The therapeutic technic is as follows: Usually during the

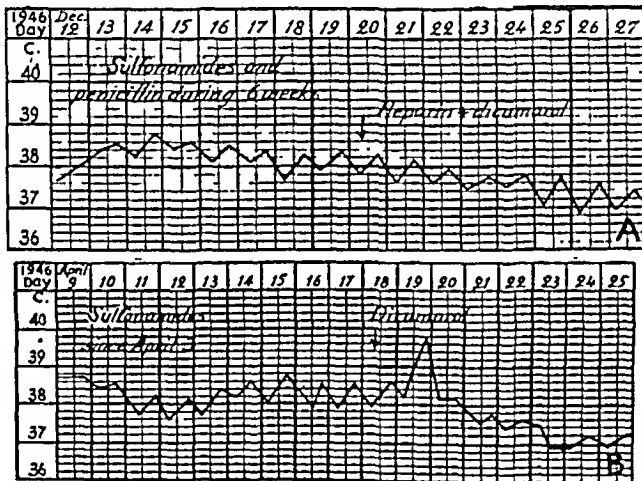


Fig. 2.—Charts of 2 patients with bronchopneumonia. A, effect of heparin and "dicumarol" on the temperature; B, effect of "dicumarol" on the temperature.

first two to three days 100 or 125 mg. of heparin is given three to four times a day together with "dicumarol." Thereafter the use of "dicumarol" is continued, so that the prothrombin index remains at approximately 30. Simultaneously with the inception of treatment the patient is allowed to move about in bed, carefully at first. Massage is then given, and movement of the lower extremities and the trunk is permitted. The "dicumarol" therapy is continued until the patient is out of bed and moving about freely.

In a number of cases "dicumarol" alone has been used. It is, however, an advantage to begin with heparin, since an anticoagulant effect is thus obtained at once instead of after two or three days. Since it is now known that the thrombi increase rapidly if untreated, it is important to prevent the growth as quickly as possible. However, the effect of "dicumarol" varies considerably. The result of a certain dose cannot be

estimated in advance, and continual control of the prothrombin index is thus necessary. The effects of "dicumarol" are particularly variable in patients in the higher age groups.

Anticoagulants have been used not only for sequelae of pneumonia but also for suspected thrombotic complication in cases of cardiac disease (chart 3), anemia and parturition, for the treatment of elderly

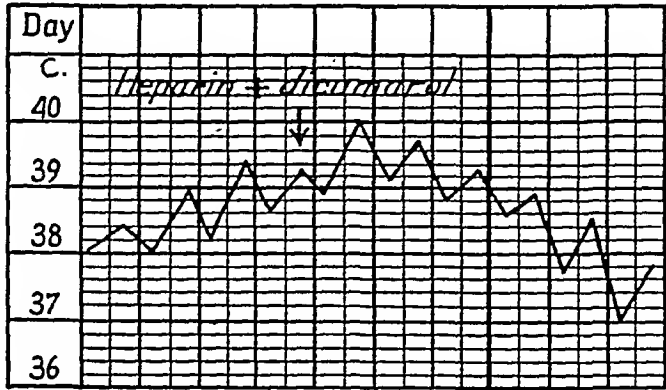


Fig. 3.—Effect of heparin and "dicumarol" on the temperature of a patient with cardiac disease.

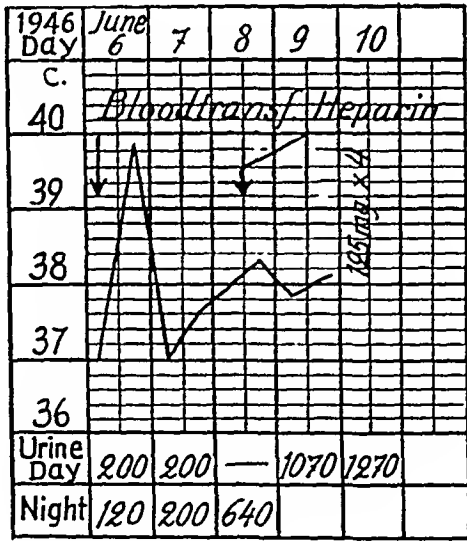


Fig. 4.—Effect of heparin on the temperature of a patient with anuria caused by Rh sensitization.

patients who have been confined to bed for a long time and in cases in which a manifest thrombosis has been present.

We have made an ever increasing use of anticoagulants in the treatment of cardiac infarctions. It is, however, too early as yet to make any statement regarding the results, since it is always difficult to predict the course of this disease.

It is well known that in chronic cardiac disease with insufficiency the tendency to thrombosis is increased. As soon as thrombosis has been

suspected heparin and "dicumarol" have been administered, and the results have been remarkable, as can be seen from the diagram.

Treatment with heparin has also been given in a number of special cases. An Rh-negative patient had received several transfusions of Rh-positive blood, which resulted in a sensitization. After the next transfusion a severe hemolytic reaction developed, with clear, red-colored urine, fever and subsequent icterus (chart 4). Anuria was present, and it could not be resolved by means of intravenous infusions. Two hours after the inception of heparin therapy the anuria cleared up, and long fibrin casts of tubuli were voided. Fibrin clots were thus precipitated in the tubules during the shock suffered by the patient in connection with the hemolysis. These clots could not, however, be retained in the tubules without a continuous precipitation of fibrin taking place. When this process was checked by the heparin, the clots loosened and the urine could once more be excreted.

The same course has been observed in cases of fibrinous bronchitis. When a tough or half solid expectorate with fibrin casts of the bronchi is observed, it is perhaps a temptation to produce a looser secretion by means of expectorants. However this results only in an increased secretion which because of the deposits of fibrin is still more troublesome. Thus, expectorants are contraindicated in such cases. Ephedrine and epinephrine should be given to relieve the bronchial spasms and heparin to decrease or counteract the deposit of fibrin. I have seen such good results from this treatment that I am tempted to characterize it as life saving.

#### SUMMARY

In cases of pneumonia the temperature sometimes does not return to normal but remains subfebrile or afebrile. The possibility of a thrombosis must be considered. The appearance of blood-streaked sputum in these cases is probably a sign of pulmonary embolism pointing to the existence of a thrombosis. In 3 such cases anticoagulant therapy with heparin and dicumarol produced rapid recovery. Heparin has been used in an instance of anuria caused by a hemolytic reaction after blood transfusion. Two hours after heparin was given the anuria cleared up. Heparin has also been successfully used together with ephedrine in cases of fibrinous bronchitis.

## HYPOPROTHROMBINEMIA

Effect of Transfusions of Blood Fortified by Administration of Vitamin K to Donors

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AND

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**H**EMORRHAGES resulting from deficiency of prothrombin can in most instances be adequately controlled by the judicious use of vitamin K. However, it was noted early<sup>1</sup> that in certain patients with severe hepatic damage the deficiency of prothrombin could not be corrected even with large amounts of vitamin K administered over long periods. It has always been assumed that the ineffectiveness of vitamin K in such patients was the result of an inadequacy of hepatic parenchyma to utilize vitamin K in the production, or activation, of prothrombin. Hemorrhage in these persons is likely, and even repeated transfusions of whole blood often will not prevent a fatal outcome.

Various types of treatment have been employed in such cases, but transfusions of whole blood have been by far the most successful. It is well known that even whole blood seldom is capable of maintaining normal levels of prothrombin much longer than a few hours. In addition to this group of cases of severe chronic hepatic damage there has recently been added the group of fulminant cases of acute infectious and serum hepatitis in which there may also develop deficiencies in prothrombin which cannot be corrected by the usual methods.

The present study was initiated by the report of Kinsey,<sup>2</sup> who apparently was observing instances of severe hepatitis with hemorrhagic manifestations which could not be controlled by administration of

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1. Brinkhous, K. M.: Plasma Prothrombin: Vitamin K, *Medicine* **19**: 329-416 (Sept.) 1940. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, *Proc. Staff Meet., Mayo Clin.* **13**: 753-764 (Nov. 30) 1938.

2. Kinsey, R. E.: A New Aid in the Control of Hemorrhage in Severe Damage to Liver: Transfusions of Blood Fortified by Administration of Vitamin K to Donors, *Arch. Int. Med.* **73**:131-137 (Feb.) 1944.



vitamin K or transfusion of whole blood. In attempting to control the hemorrhage, he administered 18 mg. of vitamin K intramuscularly to donors twenty-four hours prior to withdrawal of blood for transfusion. He reported that such blood, when administered to bleeding patients who did not respond to the usually effective measures, caused the cessation of hemorrhage and increase in the level of prothrombin in four hours. He reported 4 cases in which the patients responded in a similar manner to this form of treatment. The following study was undertaken in an effort to repeat, so far as possible, Kinsey's observation.

#### METHODS AND MATERIALS

The prothrombin time was measured by the methods of Quick as used in the Mayo Clinic<sup>3</sup>; the plasma is undiluted. The normal range varies between seventeen and nineteen seconds by this method.

The proper type of whole blood was obtained from professional blood donors and was administered within an hour after withdrawal. The blood referred to in this report as "fortified blood" was that withdrawn from a donor twenty-four hours after he had received 18.5 mg. of vitamin K intravenously. The commercial synthetic compound with vitamin K activity administered by mouth was 4-amino-2-methyl-1,4-naphthol hydrochloride, and that administered intramuscularly and intravenously was menadione bisulfite.

The patients employed in this study were all hospital patients and were suffering from severe hepatic damage, although none was actively bleeding.

#### REPORT OF CASES

CASE 1.—A man aged 53 years was admitted to the clinic on April 28, 1946, and dismissed May 15, with a diagnosis of cirrhosis of the liver. He gave a history of chronic alcoholism for six to eight years. About two or three years prior to admission, ascites developed, and at the time he had decided hematemesis; since then he had had three hemorrhages from the upper part of the gastrointestinal tract and had vomited blood. Tarry stools occurred at each episode. In December 1945, he was in hepatic coma for five days.

At the time of admission to the clinic he was semistuporous and had a strong fetor hepaticus; pulsating telangiectases were noted on the right upper eyelid, with xanthomatous patches beneath both lower lids. There was a rough systolic murmur at the apex, probably the result of early rheumatic fever. His ascites was mild, but his liver extended past the umbilicus and was rough and hard.

Laboratory examinations revealed the presence of bile in the urine; the concentration of hemoglobin was 9 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 3,870,000 and leukocytes 3,500 per cubic millimeter of blood; the routine serologic test for syphilis gave negative results. Roentgenograms of the stomach and the esophagus showed possible varices; those of the

3. Magath, T. B.: Technic of the Prothrombin Time Determination, *Am. J. Clin. Path., Tech. Supp.* 3:187-189 (Sept.) 1939.

thorax disclosed no abnormalities. Esophagoscopy showed varices involving the lower third of the esophagus. Blood smears showed moderately severe hypochromic anemia with increased regeneration. Fats in the blood were normal; the level of urea in the blood was 18 mg. per hundred cubic centimeters; serum bilirubin, delayed direct reaction with indirect bilirubin, was 2.1 mg. per hundred cubic centimeters. Serum proteins were 7.2 Gm. per hundred cubic centimeters; the albumin-globulin ratio was 1.46 to 1; a sulfobromophthalein sodium test for hepatic function disclosed grade 2 dye retention.

The prothrombin times for this patient over a period of fifteen days are shown in figure 1. He received 4 mg. of vitamin K orally for the first five days

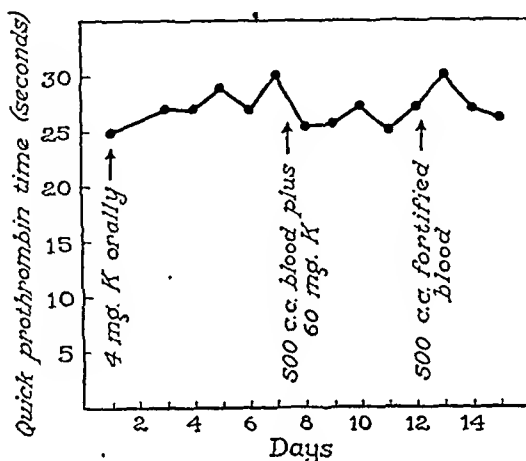


Fig. 1.—Prothrombin times in case 1.

of the study; on the seventh day he received 500 cc. of fresh whole blood, and simultaneously 60 mg. of vitamin K was administered intravenously. On the thirteenth day 500 cc. of fortified blood was administered. It will be noted that neither procedure had any appreciable immediate or delayed effect on the prothrombin time.

CASE 2.—A woman aged 58 years was admitted to the clinic April 15, 1946. She stated that since January she had had painless jaundice, which had gradually decreased. In March, she noted some discomfort in the right upper quadrant of the abdomen, and ascites slowly made its appearance. Physical examination yielded essentially negative results except for slightly icteric scleras and an enlarged abdomen filled with ascitic fluid. There were no spider angiomas and no fetor hepaticus. While she was in the hospital, a slow rise in the level of serum bilirubin occurred and pruritus and fluid in the right and left sides of the thorax developed, as well as a long prothrombin time, which did not respond to treatment with vitamin K. Paracentesis was carried out on May 8, at which time 6,500 cc. of straw-colored fluid were removed; cultures of the fluid were negative, and no malignant cells were seen.

Laboratory examination showed that the concentration of hemoglobin was 14 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 4,600,000 and leukocytes 6,400 per cubic millimeter of blood. The urine was normal; a flocculation test for syphilis gave negative results. Roentgenograms of the thorax disclosed a moderate amount of fluid in both bases; those of the stomach revealed no abnormalities. Blood smears revealed mild macrocytosis. An electrocardiogram disclosed no abnormalities. Serum bilirubin was 6.6 mg. per hundred

cubic centimeters on admission and within fifteen days had increased to 17.5 mg. per hundred cubic centimeters; there was a gradual decrease to normal levels. Serum proteins were 6.4 Gm. per hundred cubic centimeters.

It was our opinion that the most probable diagnosis was intrahepatic jaundice. Whether or not this was the result of sporadic infectious hepatitis could not be determined. The patient was dismissed from the clinic on May 17, and on November 7 she wrote to state that her ascites was not re-forming and that she was gaining weight and feeling much improved.

The results of the tests for prothrombin for this patient are illustrated in figure 2. During the first twelve days of observation she was given 4 mg. of

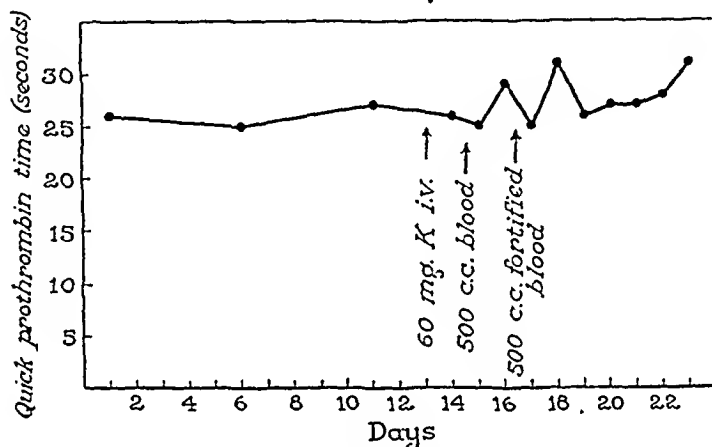


Fig. 2.—Prothrombin times in case 2.

vitamin K by mouth daily. On the thirteenth day she was also given 60 mg. of vitamin K intravenously and on the following day 500 cc. of whole fresh blood. No downward trend in the prothrombin time was noted. Two days later 500 cc. of fortified blood was administered. This was followed the next day by a tendency to longer prothrombin times.

CASE 3.—A 46 year old man was admitted to the clinic Jan. 3, 1947. He stated that in April 1944 he had undergone cholecystectomy and choledocholithotomy for stones in both the gallbladder and the duct. After operation, the jaundice cleared, but bile continued to drain through a fistula. Finally the fistula closed in November, but the patient again became jaundiced, and in December the common duct had been explored. A T tube was placed in the common duct, but bile continued to drain around the T tube for three months. Jaundice never completely cleared and had persisted to the time of admission.

Physical examination showed the patient's weight to be 161 pounds (73 Kg.); he was decidedly jaundiced, and the edge of the liver was palpable 3 finger-breadths down in the midline. Laboratory examination revealed normal urine; concentration of hemoglobin was 9.7 Gm. per hundred cubic centimeters of blood, erythrocytes numbered 4,710,000 and leukocytes 11,400 per cubic millimeter of blood; a flocculation test for syphilis and roentgenologic examination of the thorax gave negative results. The level of bilirubin in the serum was 8.5 mg., cholesterol 143 mg. and cholesterol esters 52 mg. per hundred cubic centimeters.

It was our opinion, which subsequently was confirmed by surgical intervention, that this patient had a stricture of the common duct.

The levels of prothrombin, as indicated by the tests of this patient, are shown in figure 3. It will be noted that on admission to the hospital, the prothrombin time was one hundred and sixty-four seconds and that within eight days the prothrombin time had decreased to about forty seconds, without any form of specific treatment and without vitamin K. The patient did receive intravenously, during this period, several liters of dextrose and isotonic solution of sodium chloride and a good general diet. The exact reason for this improvement of prothrombin values is not clear, but it is fairly common when one is dealing with prothrombin times of more than forty or fifty seconds in such patients. The change is reasonable when one considers that the levels of prothrombin, as indicated by a time of forty seconds and one of one hundred and sixty-four seconds, represent a difference of the order of only 10 per cent in prothrombin

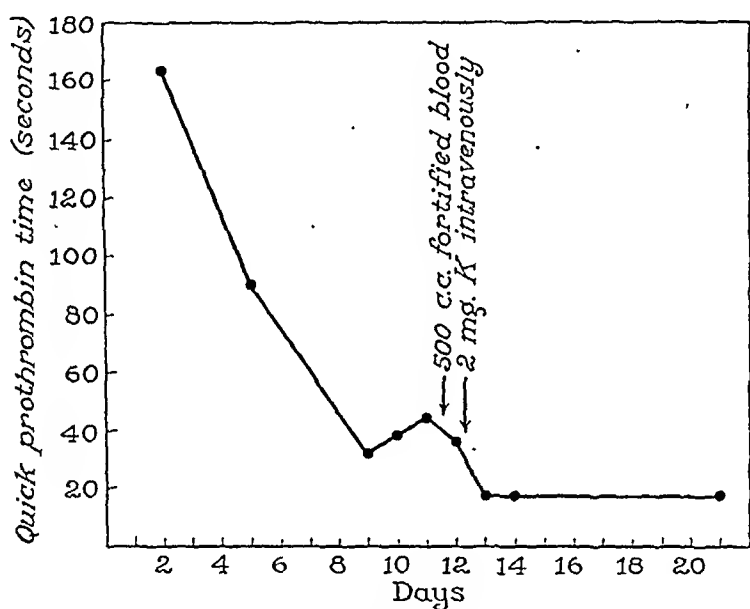


Fig. 3.—Prothrombin times in case 3.

values. The administration of 500 cc. of fortified blood, when the prothrombin time was forty seconds, was followed by only a slight fall in prothrombin time. However, on the following day, the intravenous administration of 2 mg. of vitamin K was followed by a return of the prothrombin time to a normal level.

It appears safe to conclude that neither form of treatment had any particular effect on the prothrombin level of this patient. It does illustrate how one may be deceived by results observed after applying some therapeutic agents. Had the long descending curve not been established prior to the administration of fortified blood and vitamin K, the return to normal might easily have been attributed to the use of either or both of these agents.

#### SUMMARY

Data are presented on 3 patients with severe hepatic damage, accompanied with deficiency of prothrombin in the circulating blood. Again, it has been confirmed that the deficiency of prothrombin, which frequently occurs in this type of condition, usually cannot be

corrected by administration of vitamin K or of whole blood. It also has been shown that the administration of so-called fortified blood is not effective in altering the prothrombin level in these patients. Not only was fortified blood of no value in correcting prothrombin deficiency in these patients with severe intrahepatic disease but, likewise, it was ineffectual in the correction of the deficiency in external biliary obstruction, in spite of the fact that the latter condition was quickly remedied by the administration of vitamin K alone.

# INTRAVENOUS ADMINISTRATION OF MERCURIAL DIURETICS IN MAN

Immediate Effect on the Electrocardiogram

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AND

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**D**ESPITE extensive use of mercurial diuretics by intravenous administration for many years and although fatalities following such injections have been reported, the literature contains only a few articles concerning the immediate effect of mercury on the human heart as determined by electrocardiographic tracings. In order to study this effect, the present investigation was carried out.

## METHODS

A total of three hundred and nineteen intravenous injections of mercurial diuretic preparations were administered in 137 patients. The majority of patients were hospitalized during the period of study, the remainder being ambulatory. The main diagnosis was chronic congestive heart failure in 121 cases, cirrhosis of the liver in 7, the nephrotic stage of chronic glomerular nephritis in 6 and thyrotoxicosis in 3. The patients were unselected, the only requirement for inclusion in this series being the need for diuresis.

Three different mercurial preparations were investigated. Mercurophylline injection was administered one hundred and sixty-four times, meralluride one hundred and forty-six times and mersalyl with theophylline nine times. Sixty-four patients received only one injection and 73 more than one injection. In 1 case 1 cc. of the drug was administered and in the remainder 2 cc. In a small number of cases the mercurial preparation was first diluted to 10 cc. with isotonic solution of sodium chloride or distilled water, but in most cases it was administered without dilution. No effort was made to control the rate of injection, but as a rule the duration of the injection was one to two minutes.

At least one four lead electrocardiogram (three standard limb leads and one precordial lead) was taken on each patient during the course of the investigation, but for the purposes of this study lead II only was employed. A control lead II electrocardiogram was obtained in each case immediately prior to the injection of the mercurial preparation. During the period of administration of the drug the electrocardiographic pattern was recorded continuously. Thereafter records of fifteen to twenty seconds in duration were obtained at one, two, three and four minute intervals after completion of injection.

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## RESULTS

Any significant changes observed during and after injection were considered to be a manifestation of the immediate effect of the mercurial diuretic. These included frequent auricular and ventricular premature beats, or, a definite increased frequency of these in comparison with the control electrocardiogram, and paroxysmal ventricular tachycardia. Significant electrocardiographic abnormalities were produced by the intravenous injection of mercurial diuretic preparations with thirty-six, or 11 per cent, of the three hundred and nineteen injections investigated; on 8 occasions abnormalities occurred two or more times in the same patient. Of the 137 patients investigated, significant changes were demonstrated in the electrocardiogram on 27, or 20 per cent, after intravenous administration of the drug. On 23 additional occasions the electrocardiogram taken during or immediately after the administration of the drug revealed a single auricular or ventricular

TABLE 1.—*Electrocardiographic Abnormalities Induced by the Intravenous Injection of Mercurial Diuretics*

Arrhythmia	Number of Abnormal Electrocardiograms
Auricular premature beats.....	7
Ventricular premature beats.....	26
(With bigeminy) .....	(6)
Ventricular tachycardia .....	1
Auricular and ventricular premature beats.....	2
(With bigeminy) .....	(1)

premature beat not present on the control strip. This type of change, however, was not considered definite enough to be listed as an abnormality induced by the mercurial diuretic.

One hundred and twenty-one patients of the entire group studied had chronic congestive heart failure. These patients, most of whom were receiving digitalis, were given a total of two hundred and seventy-two injections. On 31 occasions (11 per cent) abnormal electrocardiograms were produced. Six patients with the nephrotic stage of chronic glomerular nephritis were given a total of thirty-four injections, of which three (10 per cent) were followed by abnormal reactions. Seven patients with cirrhosis of the liver received ten injections, of which two (20 per cent) produced abnormal electrocardiograms. Three injections in 3 patients with thyrotoxicosis did not induce electrocardiographic abnormalities.

There was no difference in the incidence of abnormal electrocardiograms following the intravenous administration of mercurophylline injection, meralluride or mersalyl with theophylline.

The electrocardiographic abnormalities recorded during or within the first four minutes after the intravenous injection of the mercurial

compound were as follows: Auricular premature beats were found on 7 occasions and ventricular premature beats on 26; in 2 cases simultaneous disturbances of both auricular and ventricular rhythms were produced (table 1). In 5 instances the ventricular premature beats arose from different foci. Paroxymal ventricular tachycardia occurred on 1 occasion.

Of the 27 patients for whom abnormalities in the electrocardiogram were found, half were men and half were women. Twenty-three patients had chronic congestive heart failure, 2 had cirrhosis of the liver and 2 were in the nephrotic stage of chronic glomerular nephritis. The control electrocardiogram demonstrated normal rhythm in 54 instances and arrhythmia in 24 instances (table 2). Changes in the electrocardiogram were produced by meralluride on 16 occasions, by mercurophylline injection on 19 and by mersalyl with theophylline on 1. Ten patients received only one injection, while 17 were given more than one injection. For 7 of the latter group abnormalities in the electrocardiogram were produced on 2 occasions, and for 1 patient they were produced on 3 occasions. The incidence of abnormal reactions in the various diagnostic groups according to the diuretic employed and to the control rhythm prior to injection is shown in tables 3, 4 and 5.

The control rhythm prior to injection, with the possible exception of auricular premature beats, did not affect the frequency of abnormal electrocardiograms after the intravenous administration of the mercurial compounds. In 5 patients who showed significant ventricular abnormalities (4 with bigeminy and 1 with ventricular tachycardia) prior to injection no significant changes were induced. Auricular fibrillation and bundle branch block in the control electrocardiograms were not associated with an increased incidence of abnormal reactions. The control electrocardiogram showed abnormally prolonged P-R intervals in 22 cases, but this finding was not associated with a higher incidence of abnormal reactions to the mercurial injection. The P-R interval increased in some cases during or after administration of the drug, but this was not associated with a higher incidence of arrhythmias and was not tabulated as a significant change. Sinoauricular block occurred in 3 patients. Aberrant ventricular conduction was observed to follow one of five injections of meralluride in a case of congestive failure, but no other abnormalities occurred and the case is not listed in the tables. Another abnormality observed in 1 case and not classified as significant or listed in the tables was pronounced notching of the P waves after the injection of mercurophylline.

#### COMMENT

The toxic manifestations occurring after the intravenous administration of mercurial diuretic preparations have been summarized by DeGraff



TABLE 2.—Age, Clinical Diagnosis, Type of Mercurial Used and Electrocardiographic Observations in Twenty-Seven Cases in Which Abnormal Reactions Occurred

Case	Age	Diagnosis	Digitalis	Control Electrocardiogram and Number of Injections	Drug	Abnormality Observed
1	61	Cirrhosis	0	1. Normal rhythm 2. Normal rhythm	Mercuriophylline injection Mercuriophylline injection	Auricular premature beats No change
2	46	Cirrhosis	0	1. Normal rhythm	Mercuriophylline injection	Frequent auricular premature beats
3	24	Nephrosis	0	1 to 14. Normal rhythm	1. Mercuriophylline injection 2. Mercuriophylline injection 3. Mercuriophylline injection 4 to 10. Mercuriophylline injection 11 to 14. Mersalyl	No change Paroxysmal ventricular tachycardia Frequent ventricular premature beats No change
4	54	Nephrosis	0	1. Normal rhythm 2. Normal rhythm 3. Normal rhythm 4. Normal rhythm	1. Meralluride 2. Meralluride 3. Meralluride 4. Meralluride	No change No change No change Frequent ventricular premature beats
5	53	Congestive failure	+	1 to 4. Normal rhythm	1. Mercuriophylline injection 2. Mercuriophylline injection 3. Mercuriophylline injection 4. Mercuriophylline injection	Frequent ventricular premature beats No change Frequent ventricular premature beats Frequent ventricular premature beats
6	71	Congestive failure	+	1 to 5. Normal rhythm	1. Mercuriophylline injection 2. Mercuriophylline injection 3. Mercuriophylline injection 4. Mercuriophylline injection 5. Mercuriophylline injection	One ventricular premature beat No change One ventricular premature beat Frequent interpolated ventricular premature beats
7	58	Congestive failure	+	Normal rhythm	Mercuriophylline injection	Frequent ventricular premature beats
8	65	Congestive failure	+	Normal rhythm	Mercuriophylline injection	Frequent ventricular premature beats
9	81	Congestive failure	+	Normal rhythm	Mercuriophylline injection	Frequent auricular premature beats
10	67	Congestive failure	+	Normal rhythm	Mercuriophylline injection	Frequent ventricular premature beats
11	59	Congestive failure	+	Normal rhythm Normal rhythm Normal rhythm	1 to 3. Mercuriophylline injection	1. Blocked auricular premature beats 2. No change 3. No change
12	65	Congestive failure	+	1 to 4. Normal rhythm	1 to 4. Meralluride	1. No change 2. Frequent ventricular premature beats 3. No change 4. Frequent ventricular premature beats; bigeminy
13	57	Congestive failure	+	1 to 3. Normal rhythm	2 to 3. Meralluride	1. One ventricular premature beat 2. One ventricular premature beat 3. Frequent ventricular premature beats

14	51	Congestive failure	+	1 to 3, Normal rhythm	1 to 3. Mercurophylline injection	1. No change 2. Frequent ventricular premature beats 3. No change Frequent auricular premature beats
15	65	Congestive failure	+	Normal rhythm	Mercurophylline injection	No change
16	62	Congestive failure	+	Normal rhythm	1. Mercurophylline injection 2. Mercurophylline injection 3. Mercurophylline injection	One ventricular premature beat Auricular premature beats and bigeminy
17	61	Congestive failure	+	1. Normal rhythm	1. Mercurophylline injection	Frequent auricular and ventricular premature beats
18	70	Congestive failure	+	2. Normal rhythm	2. Mercurophylline injection	Frequent ventricular premature beats
19	65	Congestive failure	0	3. Auricular premature beats	3. Mersalyl	Auricular and ventricular premature beats
20	65	Congestive failure	+	Auricular premature beats Occasional auricular premature beats 1 to 4. Ventricular premature beats	Meralluride Meralluride 1 to 4. Meralluride	Frequent ventricular premature beats Many auricular premature beats
21	54	Congestive failure	+	Normal rhythm; rare ventricular premature beats	Mercurophylline injection	1. No change 2. No change 3. No change 4. Ventricular premature beats with bigeminy
22	60	Congestive failure	+	1. Auricular fibrillation and bigeminy	1. Meralluride	Frequent ventricular premature beats from different foci No change
23	39	Congestive failure	+	2. Auricular fibrillation	2. Meralluride	Ventricular premature beats and bigeminy
24	25	Congestive failure	+	3. Auricular fibrillation	3. Meralluride	Ventricular premature beats
25	64	Congestive failure	+	1 to 3. Auricular fibrillation	Meralluride 1 to 3. Meralluride	Frequent ventricular premature beats (not significant) 1. Ventricular premature beats (not significant) 2. Frequent ventricular premature beats, with bigeminy 3. Frequent ventricular premature beats
26	51	Congestive failure	+	1 to 4. Auricular fibrillation and ventricular premature beats	1 to 3. Mercurophylline injection 1 to 4. Meralluride	No change Frequent ventricular premature beats No change One ventricular premature beat (not significant) Many ventricular premature beats Many ventricular premature beats Ventricular premature beats (not significant)
27	67	Congestive failure	+	1 to 2. Auricular fibrillation and ventricular premature beats	1. Meralluride 2. Meralluride	Many more ventricular premature beats and bigeminy Many more ventricular premature beats and bigeminy

and Nadler.<sup>1</sup> The reactions may be classified into three main groups: those occurring during or within a few minutes after injection (immediate effects); those occurring at a later period and presumably due to the accumulation of mercury within the body, and those following profuse diuresis and due to sodium and chloride depletion.

TABLE 3.—*Incidence of Electrocardiographic Abnormalities in Relation to the Clinical Diagnosis*

Diagnosis	Number of Cases	Number of Injections	Number of Abnormal Electrocardiograms	Percentage of Injections with Abnormal Electrocardiograms
Chronic congestive heart failure.....	121	272	31	11
Nephrotic syndrome.....	6	34	3	10
Cirrhosis of the liver.....	7	10	2	20
Thyrototoxicosis.....	3	3	0	0

TABLE 4.—*Incidence of Abnormal Electrocardiograms in Relation to the Mercurial Preparation Employed*

Preparation	Number of Injections	Number of Abnormal Electrocardiograms	Percentage of Abnormal Electrocardiograms
Mercuriophylline injection.....	164	19	11
Meralluride.....	146	16	11
Mersalyl with theophylline.....	9	1	11

TABLE 5.—*Incidence of Abnormal Electrocardiograms in Relation to the Initial Cardiac Rhythm*

Initial Rhythm	Number of Patients	Number of Injections	Number of Abnormal Electrocardiograms	Percentage of Abnormal Electrocardiograms
Normal rhythm .....	78	180	20	11
Normal rhythm with intraventricular block.....	11	26	3	11
Auricular premature beats.....	6	9	3	33
Auricular and ventricular premature beats.....	1	2	0	0
Ventricular premature beats.....	9	22	2	9
Ventricular premature beats with bigeminy.....	2	2	0	0
Auricular fibrillation .....	20	53	6	10
Auricular fibrillation with ventricular premature beats	7	17	2	12
Auricular fibrillation with bigeminy.....	2	2	0	0
Ventricular tachycardia .....	1	1	0	0

The immediate toxic reactions reported have consisted of sudden death, sudden dyspnea, palpitation, fainting, convulsions, apprehension, collapse, cyanosis, orthopnea and transitory pain in the chest.<sup>2</sup> The

1. DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of the Mercurial Diuretics in Man, J.A.M.A. **119**:1006 (July 25) 1942.

2. Wexler, J., and Ellis, L. B.: Toxic Reactions to the Intravenous Injection of Mercurial Diuretics, Am. Heart J. **27**:86, 1944.

explanation of these phenomena has been varied and controversial. Although sudden death following the intravenous administration of a mercurial diuretic has been attributed to anaphylactic shock<sup>3</sup> and to speed shock,<sup>4</sup> it is now commonly believed that the various immediate reactions are similar in nature and are a result of cardiac arrhythmias produced by mercury.<sup>2</sup> This conclusion is supported by animal experimentation in which a variety of cardiac arrhythmias have been produced by the perfusion of isolated hearts with solutions containing mercury or by the intravenous injection of mercurial preparations into anesthetized dogs and cats.<sup>5</sup>

Investigations of the immediate effect of the mercurial diuretics on the human heart have been few. Bloom and Cashon<sup>6</sup> studied the effect of mersalyl on 20 patients without cardiac disease by recording electrocardiograms before the intravenous injection of 2 cc. of the drug and fifteen and thirty minutes after. No significant abnormalities were produced. Since the immediate toxic reactions reported have occurred within ten minutes after injection, it would appear that the interval between the control electrocardiogram and that taken after administration of the drug was too long and that significant immediate changes might have been missed. Volini, Levitt and Martin<sup>7</sup> reported sudden death following the intravenous administration of "esidrone" (the sodium salt of pyridenedicarboxyl-beta-mercuri- $\gamma$ -hydroxypropylamide and theophylline) in 2 cases in which electrocardiograms taken during and after the administration of the drug showed the development of fatal ventricular fibrillation. Ventricular premature beats were recorded electrocardio-

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3. Wolf, I. J., and Bongiorno, H. D.: Sudden Death with Salyrgan, *Canad. M.A.J.* **25**:73, 1931. Greenwald, H. M., and Jacobson, S.: Sudden Death Due to Mercurial Diuretics, *J. Pediat.* **11**:540, 1937. Tyson, M. C.: Danger of Intravenous Mercurial Injections in Nephrosis, *J.A.M.A.* **117**:998 (Sept. 20) 1941. Vaughn, J.: Immediate Fatality Following Use of Mercupurin, *J. Pediat.* **21**:680, 1942.

4. Hyman, H. T.: Sudden Death After Use of Mercurial Diuretics, Correspondence, *J.A.M.A.* **119**:1444 (Aug. 22) 1942.

5. Salant, W.: The Pharmacology of Mercury, *J.A.M.A.* **79**:2071 (Dec. 16) 1922. Jackson, D. E.: The Pharmacological Action of Mercury in Organic Combination, *J. Pharmacol. & Exper. Therap.* **29**:471, 1926. McCrea, F. D., and Meeks, W. J.: The Action of Mercury upon the Heart, *ibid.* **36**:295, 1929. Johnston, R. L.: Cardiac Depression by Mercurial Diuretics, *J. Lab. & Clin. Med.* **27**:303, 1941. DeGraff, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics, *J.A.M.A.* **119**:998 (July 25) 1942. Barker, M. M.; Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics, *ibid.* **119**:1001 (July 25) 1942.

6. Boom, N., and Cashon, G.: The Effect of Salyrgan (Mersalyl) on the Electrocardiogram, *Virginia M. Monthly* **62**:216, 1935.

7. Volini, I. F.; Levitt, R. O., and Martin, R.: Studies on Mercurial Diuresis: Sudden Death Following Intravenous Injection; Report of Three Cases, with Electrocardiographic Studies in Two, *J.A.M.A.* **128**:12 (May 5) 1945.

graphically on 1 patient by Ben-Asher immediately after the intravenous administration of a mercurial diuretic.<sup>8</sup>

The results of the present investigation show that disturbances in cardiac rhythm in man commonly follow the intravenous administration of mercurial compounds. The preponderance of ventricular abnormalities observed in this study indicates that the ventricle is much more susceptible to the action of mercury than is the auricle. Although no deaths occurred in the present series, the possibility that the disturbances in cardiac rhythm induced by the drug might progress into a fatal or severe arrhythmia is always present.

It is not possible to predict which patients will have immediate reactions after the intravenous administration of mercurial compounds. There is no evidence that dilution or changing from one preparation to another will prevent such reactions.<sup>2</sup> The results of this study indicate that there is no difference in the incidence of toxic reactions produced by mercuriophylline injection, meralluride or mersalyl with theophylline. The cardiac mechanism prior to injection, with the possible exception of auricular premature beats, does not affect the incidence of electrocardiographic abnormalities induced by the drug. There is no difference between the frequency of arrhythmias produced in patients with chronic congestive heart failure and that produced in patients with the nephrotic stage of chronic glomerular nephritis. The number of injections given in cases with cirrhosis of the liver studied is too small to permit of any definite conclusion in this regard. Untoward reactions frequently occur even though previous injections were uneventful; the reverse may be observed. Digitalis does not predispose to the production of arrhythmias after the intravenous injection of mercurial diuretics.

#### SUMMARY

The immediate effects of the intravenous injection of mercurial diuretics on the human heart were investigated by means of electrocardiograms taken before, during and at short intervals after the injection of mercuriophylline, meralluride and mersalyl with theophylline in 137 patients. Three hundred and nineteen individual observations were made, and in thirty-six of these significant electrocardiographic abnormalities were produced. The mercurial preparation employed, the presence or type of cardiac disease, the age of the patient, the use of digitalis and the cardiac rhythm prior to injection did not affect the incidence of the production of abnormalities. These abnormalities consisted of various disturbances in cardiac rhythm; no fatalities occurred in this series.

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8. Ben-Asher, S.: On the Toxicity of the Mercurial Diuretics: Observations on Eighteen Cases with Suggestions for the Prevention of Toxic Reactions. *Ann. Int. Med.* 25:711, 1946.

# MENINGOCOCCIC BACTEREMIA

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FROM September 1940, when mobilization for World War II began, to August 1945 about 14,500 soldiers with meningococcic infections were treated in army hospitals.<sup>1</sup> This preliminary count is based on periodic summary reports in which bacteremia and meningitis are not differentiated, so that the exact number of cases of each form of the infection is not known. It is estimated, however, that not less than 5,000 soldiers were admitted with bacteremia uncomplicated by meningitis or with bacteremia prior to localization in the meninges.<sup>2</sup>

It is the purpose of this paper to describe meningococcic bacteremia as it was seen among soldiers during World War II and to illustrate in a report of cases the various forms which the disease assumed. Since the fatality rate for all types of meningococcic infection in the army during World War II was less than 5 per cent, it seems worth while to review the methods of treatment used.

The meningococcus probably invades the body from the nasopharynx, and infection in this region may or may not be indicated by clinical disease. The subsequent manifestations are those of sepsis and localization. During World War I, Herrick<sup>3</sup> and others showed that the course of events consists of an invasion of the blood stream and, if not prevented by spontaneous resistance or therapy, of localization in the meninges, joints, skin, eyes or other body tissues.

It is essential to view the disease as a generalized infection that is sometimes overshadowed by the advent of the more dramatic symptoms of meningitis or fulminant bacteremia. It is highly important that the stage of bacteremia be recognized early and that the patient be treated promptly, for in this way the disease can usually be terminated before localization in the meninges occurs. If meningitis does supervene in spite of early treatment, the advantages of prompt therapy have been

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1. Data Assembled for the Author by the Medical Statistics Division, Office of the Surgeon General, United States War Department, Washington, D. C.

2. Reports from various station hospitals in the United States, where careful studies were carried out, indicate that about one third of the patients were suffering from bacteremia without meningeal involvement at the time of admission.

3. Herrick, W. W.: Early Diagnosis and Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis. *J. A. M. A.* **71**:612 (Aug. 24) 1918.

afforded. In a large series of patients with meningococcic infection the disease was recognized in the stage of bacteremia in 35 per cent.<sup>4</sup>

Meningococcic bacteremia began, as a rule, with prodromal symptoms of disease of the upper respiratory tract. After an indefinite period of from a day to a week or more, the manifestations became more acute. There was usually a sudden chill, with rapid rise in temperature, but the onset was occasionally gradual. Malaise, extreme weakness, aching of muscles, moderate headache, nausea, vomiting, pains in the joints or actual acute inflammation of joints developed. The most characteristic manifestation was the rash. Its presence was essential to clinical diagnosis prior to the advent of meningeal localization. The rash was at times so sparse that careful and frequently repeated search was necessary to find it, but often it was obvious and noted by the patient. A wide variety of forms of rash occurred, and knowledge of the variations was essential to the recognition of the disease. The commonest lesion was petechial or purpuric and varied from 1 to 15 mm. in diameter (fig. 1 *A*). In addition to this type, which has been emphasized in the past, other forms of rash not commonly described were generally seen. Ill defined faint pink macules similar to the rose spots of typhoid fever were common (fig. 1 *B*). Sometimes these were evanescent, and not infrequently a scattered few constituted the only cutaneous manifestation. Maculopapular lesions (fig. 2 *A*) were usually present, and in some instances they had a central petechia. The larger ones of this type were nodular or plaquelike (fig. 2 *B*) and often tender. When on the extremities, these nodules bore a striking resemblance to the smaller lesions of erythema nodosum. Combinations of the cutaneous manifestations occurred, and indeed most patients showed more than one type of lesion. The petechiae occasionally were present in the conjunctivas and in the oral mucous membranes. The rash occurred anywhere on the body but usually spared the face and was less common on the palms and soles. It often occurred in crops. The macular lesions sometimes receded with fall in temperature, only to reappear as the temperature again rose. The rapidity with which the rash often appeared made it necessary to examine carefully every patient suspected of having the disease at hourly intervals. It could advance from a few vague spots to a widespread eruption in a few hours. Some ecchymotic lesions became vesicular, and ulceration occasionally occurred. The rapid disappearance of the maculopapular component of the rash within twelve to eighteen hours after the beginning of sulfadiazine therapy was almost diagnostic of meningococcic bacteremia. In fulminant bacteremia a broadspread, extensive ecchymotic rash

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4. Daniels, W. B.; Solomon, S., and Jaquette, W. A., Jr.: Meningococcic Infection in Soldiers, *J. A. M. A.* **123**:1 (Sept. 4) 1943.

developed (fig. 4). This in some cases involved 80 per cent of the body. Large areas of hemorrhage developed beneath the conjunctivas and the oral mucous membranes in a few patients.



Fig. 1.—*A*, pink macules and the common petechial and purpuric lesions of the skin in a patient with bacteremia. *B*, flat pink macules resembling the rose spots of typhoid in a patient with bacteremia.

Herpes simplex was common, usually occurring about the second day of the illness. Herpes zoster involving the ophthalmic and maxillary branches of the fifth cranial nerve was observed.



The temperature of patients admitted with meningococcemia ranged from 97 to 106 F. It was generally between 101 and 102 F. Leukocytosis (15 to 50,000 cells per cubic millimeter) with an increase in polymorphonuclear cells was the rule, but in a few cases the leukocyte count was normal.

#### VARIATIONS IN MENINGOCOCCEMIA

There was a simple acute form of meningococcemia, with fever, malaise, pains in joints, rash and leukocytosis. The progress of this



Fig. 2.—*A*, raised pink and purplish papular and nodular lesions with a few scattered purpuric ones in a patient with bacteremia. *B*, flat pink macules and plaque-like lesions on the skin in a patient with bacteremia.

type could be arrested in this stage by sulfadiazine therapy, as illustrated in the first case.

CASE 1.—A soldier aged 34 years had had a slight cold for about two weeks before his admission to the hospital. During the afternoon of the day prior to his admission he rather suddenly began to feel unusually tired and to ache all over. During the night he had chilly sensations alternating with feverishness, and in the morning he had a moderately severe headache. He was acutely but not

seriously ill. His face was flushed, and his temperature was 101.3 F. There was slight inflammation of the nose and throat, and a maculopapular rash was scattered over the trunk and all extremities. The neurologic system was entirely normal. The white blood cell count was 19,800 per cubic millimeter, with 81 per cent polymorphonuclear leukocytes. Blood cultured on admission yielded type I meningococci. No lumbar puncture was done. As soon as the blood for culture had been taken sulfadiazine was given by mouth. The temperature was normal within two days. No signs of meningitis developed.

The disease at times was relatively mild and subacute, so that the fever, malaise, pains in joints and rash suggested rheumatic fever, erythema multiforme or some other infection. The following case is illustrative.

CASE 2.—A soldier aged 21 years had been well until three days before his admission to the hospital, when he suddenly had a shaking chill, with the development of fever, malaise and sore throat. The only significant findings were a few erythematous blotches on the chest and the legs and a palpable spleen. There was a continuous fluctuating fever during the succeeding eleven days. A rash consisting of macular, papular and nodular lesions with a few petechiae appeared in crops. Shortly after his admission redness, tenderness and swelling of the right ankle developed. The blood leukocyte count was 16,300 per cubic millimeter, with 73 per cent polymorphonuclear cells. Many erythrocytes were noted in several specimens of urine. The spinal fluid was normal. Blood cultures yielded type IIA meningococci. After the first dose of sulfadiazine by mouth, the temperature became normal and remained so. The rash faded promptly.

The extraordinarily mild character which meningococcic infection occasionally assumed is illustrated by the following case.<sup>5</sup>

CASE 3.—The 10 year old son of an officer was admitted to an army hospital with minimal headache and fever (temperature, 100 F.). Admission was granted only on the insistence of his apprehensive mother, who feared poliomyelitis. Because of pressure from the mother, examination of the cerebrospinal fluid and blood culture were carried out. The spinal fluid cell count was normal. Two days later both the blood and the spinal fluid were shown to contain *Neisseria intracellularis*. At this time one cutaneous lesion thought to be a small petechial hemorrhage was found on careful scrutiny. A second examination of the spinal fluid showed it to be normal. Culture of blood drawn on the third day again yielded meningococci. Since the patient had become afebrile and asymptomatic, no sulfonamide compounds were given. Subsequent blood cultures were sterile. For ten days the patient was watched closely, and no recurrence of symptoms and no manifestations of illness developed. At this time a course of sulfadiazine therapy was started. The patient was discharged well after approximately three weeks' observation.

It is probable that during the periods of increased prevalence of meningococcic infection some cases in which there was illness of mild character due to the presence of *N. intracellularis* were not detected and the patients recovered spontaneously. A number of patients were observed to recover from meningococcic bacteremia after minimal

5. Turner, R. H.: Personal communication to the author.

amounts of a sulfonamide compound had been given. In some instances the total dose was as little as 2 Gm. These patients usually had a mild illness, with fever, and were given a single dose of sulfadiazine by the ward officer, after which no more of the drug was administered. Later the original blood cultures taken before therapy were shown to contain *N. intracellularis*, but the patients had by then become free of abnormal symptoms.

In other patients the course was chronic and produced a persistent, low grade febrile illness. In the following case it was not severe enough to prevent the patient from continuing military duty.

CASE 4.—A soldier aged 23 years was admitted to the orthopedic service because of an injured ankle. It was learned that for about three weeks he had been suffering from malaise, evening feverishness and an intermittent eruption of red nodules on his legs. While he was in the hospital his temperature ranged from normal to 102 F. There was migrating arthralgia, and a scattered erythematous papular rash appeared. This was most apparent on the extremities. The leukocyte count was 12,600 per cubic millimeter, with 81 per cent polymorphonuclear leukocytes. Two blood cultures yielded type I meningococci. There were no meningeal symptoms or signs at any time, and the spinal fluid was normal. All manifestations cleared entirely within twenty-four hours after sulfadiazine was administered by mouth. The illness had been of four weeks' duration prior to treatment.

#### TRANSITION FROM BACTEREMIA TO MENINGITIS

The recognition of meningococcic sepsis before invasion of the meninges occurred was relatively easy during the epidemic, when the index of suspicion was high. It is in the sporadic case that delay in diagnosis and treatment is likely.

CASE 5.—A private aged 20 years was admitted to the hospital with a history of sore throat which had been present for one week. On the day before his admission there was a sudden onset of shaking chills, fever and painful joints. There were a few small erythematous nodular lesions of the skin, and the pharynx showed mild inflammation. Both knees, both elbows and the right wrist and ankle were tender and warm but not red or swollen. The blood leukocyte count was 11,500 per cubic millimeter, with 78 per cent polymorphonuclear cells. A tentative diagnosis of acute rheumatic fever was made and full dosage of salicylates prescribed. In spite of this medication the temperature ranged from normal to 102.4 F. for the succeeding thirteen days. On the thirteenth day in the hospital there was a sudden rise in temperature to 105 F., with severe headache, nausea and vomiting. Within three hours the patient was stuporous and presented all the signs of severe meningitis. A dozen or so pinkish macules resembling rose spots were present on the trunk at this time. The spinal fluid contained 1,200 white blood cells per cubic millimeter, with 95 per cent polymorphonuclear leukocytes. Treatment with sulfadiazine resulted in recovery. It was begun before blood was taken for culture, which showed no growth.

The next case illustrated the importance of cutaneous manifestations and how the absence of a persistent rash during the greater part of the stage of sepsis delayed diagnosis.

CASE 6.—The patient was admitted to the ward for patients with diseases of the respiratory tract, having had a cold with nasal congestion, slight cough and sore throat for one week. During the day before his admission he had several slight chills and felt feverish. He vomited once. Examination revealed moderate inflammation of the nasopharynx and a discrete macular rash on the trunk and around the shoulder girdle, which disappeared within a few hours. For about eleven days the range of temperature was of the "septic" type, with daily elevations to 102 F. associated with polymorphonuclear leukocytosis. He complained of intermittent pain in the popliteal spaces, and it was thought that the tip of the spleen was palpable. A diagnosis of subacute bacterial endocarditis was suggested, and repeated blood cultures were made. Ten days after his admission to the hospital the temperature rose to 103 F. and he appeared worse. There were no meningeal signs or symptoms. On the next day increasingly severe headache developed, with nausea and vomiting. Examination revealed a slightly stiff neck, a positive Kernig sign and sparse petechiae on the upper part of the trunk. The spinal fluid was cloudy and contained 9,700 cells per cubic millimeter; smear and culture showed the presence of type I meningococci. The blood taken on the day before the development of meningeal signs later yielded the same organism. Recovery was rapid on sulfadiazine therapy.

The speed with which meningitis could develop in a patient with meningococcemia was extremely variable. The next case to be reported was one in which early meningitis was present on the patient's admission to the hospital as indicated by recovery of meningococci on culture from an otherwise normal spinal fluid. The history, however, gave clearcut evidence that a state of sepsis existed for about twenty-four hours before admission. This case also illustrated how rapidly meningitis can advance in spite of prompt and adequate sulfadiazine therapy.

CASE 7.—A private aged 37 years was well until the day before his admission to the hospital. During the morning of that day he suddenly had a shaking chill and began to feel extremely weak. Headache was moderately severe, but it subsided during the evening. On the morning of the day of admission the headache was gone, but he noticed that he was covered with tiny dark purplish spots. His right knee was moderately painful on walking. Severe frontal headache again developed on his admission to the ward. He was obviously acutely and seriously ill although he was alert and well oriented. Scattered over the trunk and all extremities were myriads of dark petechiae, all less than 2 mm. in diameter. There was no stiffness of the neck, and Kernig and Brudzinski signs were not present. A specimen of spinal fluid contained 3 lymphocytes per cubic millimeter and a normal amount of sugar, and it yielded no organisms on smear. By the following day, however, type I meningococci had grown in this fluid. Immediately after the initial lumbar puncture 5 Gm. of sodium sulfadiazine was given intravenously with 1,500 cc. solution of sodium chloride and dextrose.

Four hours after the patient's admission to the hospital projectile vomiting developed and he rapidly became stuporous. All the signs of meningitis were present to a high degree. Five and one quarter hours after the first lumbar puncture another specimen of spinal fluid was obtained. The fluid was under greatly increased pressure and contained 17,700 leukocytes per cubic millimeter, with 99 per cent polymorphonuclear cells. The concentration of sugar had fallen to a level too low to be read with accuracy, and the level of sulfadiazine had reached 8.2 mg. per hundred cubic centimeters. Smear and culture of this second specimen

showed no meningococci in spite of the addition of paraaminobenzoic acid to the culture mediums.

After an extremely stormy course the patient recovered. Though the blood culture was contaminated on his admission to the hospital and no meningococci were found, the history of a shaking chill, the presence of a purpuric rash extensive enough to be noticed by the patient and a painful knee joint, all at a time when he was entirely free of headache, were believed to be evidence that invasion of the blood stream occurred several hours prior to his admission. That meningitis was in the earliest phase at the time of admission was shown by the fact that the spinal fluid was normal in every respect except that meningococci were grown on culture. There were no meningeal signs present except for severe headache.

#### FULMINANT MENINGOCOCCIC BACTEREMIA

There was a form of fulminant, rapidly fatal meningococcic sepsis in which there was little or no evidence of meningitis either during life or at autopsy and in which the clinical manifestations were not those of the Waterhouse-Friderichsen syndrome. At autopsy the adrenals were not abnormal. The rash was broadspread and frequently as extensive as that in patients who had massive bilateral hemorrhage into the adrenals. The following is an illustrative case.

CASE 8.—A 20 year old soldier was admitted to the hospital at 4:30 a. m. after a few hours of illness with chills, fever, headache and weakness. On his admission the temperature was 107 F. Stupor was marked. The pulse was strong, pounding and rapid, and the blood pressure was 120 systolic and 70 diastolic. There was no stiffness of the neck or other evidence of meningeal irritation. Scattered broadly over the skin were myriads of petechial and purpuric lesions, some of which coalesced to form areas of ecchymosis. The cerebrospinal fluid was normal. A blood culture later yielded type I N. intracellularis. Four grams of sodium sulfadiazine was promptly given intravenously. Stupor deepened, and only terminally did cyanosis develop. Death occurred eight hours after his admission to the hospital.

At autopsy neither the adrenals nor the leptomeninges showed abnormality. There were small scattered hemorrhages throughout most of the organs.

Instances of a fatal form of fulminant bacteremia associated with so-called "tubular degeneration of the adrenals" as described by Rich<sup>6</sup> have occurred among army personnel. The adrenals in these instances are not the site of hemorrhage. Meningitis may or may not be present. The case reported by Kinsman, D'Alonzo, and Russi<sup>7</sup> is illustrative.

CASE 9.—A 29 year old white soldier was admitted to the hospital at 3:30 p. m. on Jan. 22, 1944, about two hours after the sudden onset of weakness, shaking chills, fever, headache, pain in the back and exhaustion. The temperature on

6. Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections and Its Possible Relation to Circulatory Collapse, *Bull. Johns Hopkins Hosp.* **74**:1, 1944.

7. Kinsman, J. M.; D'Alonzo, C. A., and Russi, S.: Fulminating Meningococcic Septicemia Associated with Adrenal Lesions: Analysis and Discussion of Seven Cases, *Arch. Int. Med.* **78**:139 (Aug.) 1946.

admission was 104.6 F. The leukocyte count was 11,950, with 84 per cent neutrophils. Physical examination revealed nuchal rigidity of minimal degree, but Kernig's sign was absent. The pharynx was moderately infected. Group I meningococci were later recovered from the spinal fluid. Early the next morning (January 23) an increasingly widespread, mottled purpuric and ecchymotic rash developed over the entire body including the face and neck, about 80 per cent of the body surface eventually becoming involved. There were scattered hemorrhagic spots, most of which were an inch (2.5 cm.) or more in diameter. These were also present in the conjunctivas and in the mouth. The uvula was completely black from hemorrhage. In spite of treatment the eruption continued to spread. The patient became restless and complained of chilliness, burning and soreness "in the spots." His lips, finger nails and entire skin became cyanotic; the pulse was 110 and the blood pressure 130 systolic and 100 diastolic. Nuchal rigidity had not increased, and Kernig's sign was still absent. The leukocyte count was 27,200, with 87 per cent neutrophils. The temperature was 105 F. At 1:10 p. m. he became comatose and cyanotic, with rapid respirations. The temperature climbed to 107.8 F., and the respirations dropped to 8 per minute. A direct smear of the blood showed diplococci phagocytosed by neutrophils. The blood culture was later reported to contain meningococci of group I. In spite of all therapy the patient died at 3:10 p. m., twenty-six hours after the onset of illness. A second spinal puncture was done at the time of the autopsy, and the fluid contained 2,200 cells. Autopsy revealed widespread focal hemorrhages in the pulmonary parenchyma and petechial hemorrhages in the pleura, pericardium and endocardium. There were no hemorrhages in the adrenals. Microscopically there was notable congestion of the sinusoids but no extravasation. The cells in the glomerular zone displayed a vacuolated cytoplasm and appeared of average size, while those in the inner part of the fascicular and reticular zones had shrunk, their cytoplasm being homogeneous, dark and sprinkled with brown pigment. In this case the "tubular" changes in the outer half of the fascicular layer were prominent. The lesion was identical with that described by Rich. The cords in the outer third of the fascicular zone were converted into tubules lined by vacuolated cells, many of which had undergone degeneration with fraying of the cytoplasm and pyknotic changes of the nuclei. In some instances the adrenal cells had disappeared entirely from the inner layer of the cortex, leaving only a reticular stroma between the congested capillaries. The medulla was not remarkable (fig. 3).

The meninges were not conspicuously involved on gross examination. Microscopically there was a fair amount of acute inflammatory cellular exudate in the subarachnoid space.

Fulminant meningococcic bacteremia without meningitis and with the clinical manifestations of Waterhouse-Friderichsen syndrome occurred in this case, and yet no hemorrhage or other abnormality of the adrenals was found at autopsy. Four such cases were found among 300 fatal cases analyzed.<sup>8</sup> In a number of others the history suggested this syndrome, but the clinical abstracts were not detailed enough to allow reliable deductions to be drawn. Thomas<sup>9</sup> has reported 3 such cases.

8. Daniels, W. B.: The Cause of Death in Three Hundred Fatal Cases of Meningococcic Infection, to be published.

9. Thomas, H. M.: The Treatment of Fulminating Meningococcic Infections, Bull. U. S. Army M. Dept., 1944, no. 73, p. 78.

CASE 10.—A soldier aged 21 years suddenly became ill twenty-four hours prior to his admission to the hospital with severe headache, stiffness, generalized aching, nausea and vomiting. Aside from fever, dusky cyanosis and petechiae scattered over the skin, the examination revealed nothing abnormal. About eighteen hours after his admission he became rapidly worse in spite of a sulfadiazine blood concentration of 9 mg. per hundred cubic centimeters; the cutaneous eruption spread, and pallor with cyanosis became extreme. The extremities were clammy, and there was evidence of considerable shock. A blood culture yielded *N. intracellularis*. Stained films of the peripheral blood showed diplococci within

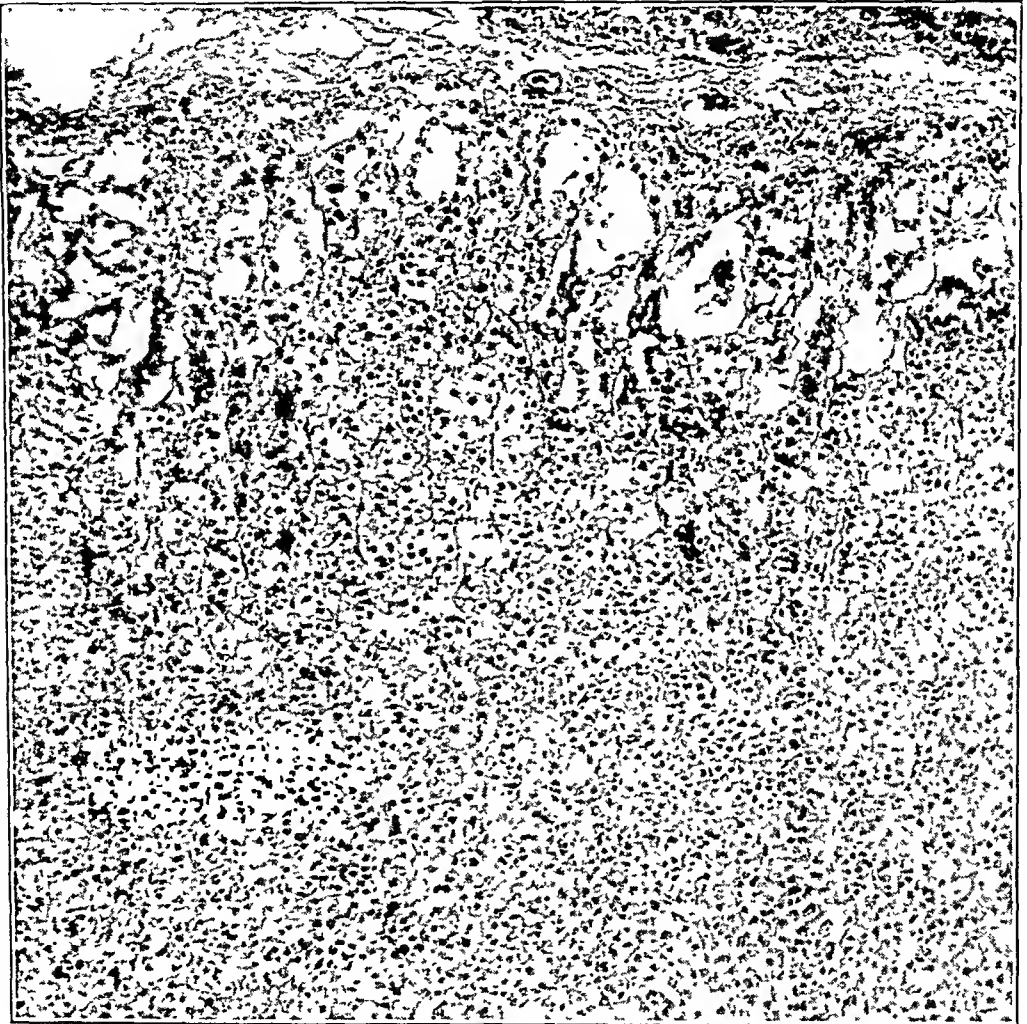


Fig. 3.—Photomicrograph showing tubular degeneration of the adrenal in a patient with fulminant bacteremia;  $\times 15$ . (Army Institute of Pathology negative no. 99742.)

the leukocytes, and smears from punctured purpuric cutaneous lesions revealed gram-negative diplococci. The patient died in shock thirty hours after his admission to the hospital.

The autopsy revealed no adrenal hemorrhage or evidence of meningitis. Petechiae were scattered over all serous surfaces. The interstitial tissues of the myocardium showed a diffuse infiltration with polymorphonuclear leukocytes.

Among 300 fatal cases of meningococcic infection studied, 10 per cent of patients died as the result of fulminant bacteremia without adrenal hemorrhage. Thirteen of these had no meningitis, 16 had slight meningitis and for 1 autopsy records were incomplete. The average duration of life after admission to the hospital was thirty-three hours, with a range of from two to one hundred and one hours. In 4 of the patients the symptoms satisfied all the clinical criteria of the Waterhouse-Friderichsen syndrome, but at autopsy the adrenals were not abnormal. The average duration of life in the 4 cases, was forty hours after admission to the hospital.<sup>8</sup>

Fulminant meningococcic bacteremia with peripheral vascular failure and hemorrhage into the adrenal at autopsy, i. e., the so-called Waterhouse-Friderichsen syndrome, was described first in 1894 by Voelcker.<sup>10</sup> Additional cases were later reported by the authors whose names the syndrome bears.<sup>11</sup> No more dramatic or catastrophic situation requiring heroic therapy can face the physician.

From the beginning of the epidemic in December 1942 patients with this syndrome were admitted to army hospitals. Some died rapidly before specific treatment was instituted. Considering the rarity of the disease, it is not surprising that in 14 (11 per cent) of 126 fatal cases the condition was misdiagnosed or not diagnosed prior to necropsy.<sup>9</sup> The antemortem diagnoses were as follows: rocky mountain spotted fever in 3 cases, heat stroke in 2 cases, purpura hemorrhagica in 2 cases, endemic typhus in 1 case, acute leukemia in 1 case and pachymeningitis in 1 case. In 4 cases no diagnosis was made. A few more than 100 instances of this form of meningococcic infection had been reported prior to the war. Since meningococcic meningitis, bacteremia and the Waterhouse-Friderichsen syndrome are coded together by the Statistical Division of the Surgeon General's Office, it is impracticable to ascertain the exact number of soldiers who were affected with each form of the disease during the war.

In two series of 214 and 182 patients with meningococcic infection recently reported, the Waterhouse-Friderichsen syndrome occurred in 3.3 and in 2.2 per cent respectively.<sup>12</sup> The records of 300 of the soldiers who died as the result of meningococcic infection from the beginning of mobilization to Dec. 31, 1945, were reviewed at the Army Institute of Pathology. One hundred and twenty-six (42 per cent) of these died

10. Voelcker, A. F.: Pathological Report, 1894, Middlesex Hospital Reports, 1894, p. 279.

11. Waterhouse, R.: Case of Suprarenal Apoplexy, *Lancet* 1:577, 1911. Friderichsen, C.: Nebennieren-apoplexie bei kleinem Kindern, *Jahrb. f. Kinderh.* 87:109, 1918.

12. (a) Bernhard, W. G., and Jordon, A. C.: Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome) Associated with Meningococcal Septicemia: Report of Four Cases in Adults with Review of the Literature, *J. Lab. & Clin. Med.* 29:357, 1945. (b) Kinsman, D'Alonzo and Russi.<sup>7</sup>



with hemorrhage into the adrenals.<sup>8</sup> More than 50 instances of this syndrome have been recently reported in the literature by army medical officers. This is an incomplete list, as many cases were reported only because of unusual features, long survival period or recovery.<sup>13</sup>

Meningitis was usually absent or slight in this group of patients. Of 126 patients who died with fulminant bacteremia and had hemorrhages into the adrenals at autopsy, there was no evidence of meningitis in 61, in 48 the meningitis was early and minimal, in 7 it was moderately severe and in another 7 it was severe. In 3 cases the grade of meningitis was not clear from the records. Early death may have been responsible for minimal or absent meningeal inflammation.

As with other meningococcic infections, prodromal respiratory symptoms usually preceded the onset. These were followed by general aching, pains in the joints, headache, weakness, nausea, vomiting, chills and fever. Within a few hours there was a dramatic, sudden change, with the development of apprehension, restlessness and frequently an initial delirium. Later the patients were often lucid. A previously insignificant rash suddenly became widespread, purpuric and ecchymotic and often covered two thirds of the body. The conjunctivas and the buccal mucous membranes showed hemorrhages. As a rule there were no signs of involvement of the meninges, but meningitis, usually of mild degree, might be present. Cyanosis, low blood pressure, rapid, thready or imperceptible pulse, cold wet extremities and all evidences of extreme shock supervened. Anuria with nitrogen retention was usual. Within a few hours to a day or more pulmonary edema usually developed, and death generally occurred in spite of heroic therapy. In fatal cases the average duration of life from the time of admission to the hospital until death occurred was twenty-four hours.<sup>8</sup>

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13. (a) Wright, D. O., and Reppert, L. B.: Fulminating Meningococcemia with Vascular Collapse: Report of Four Adult Cases with Recovery, *Arch. Int. Med.* **77**:143 (Feb.) 1946. (b) Kosich, M., and Disick, S.: Meningococcemia with Bilateral Adrenal Hemorrhage, *J. Tennessee M. A.* **36**:464, 1943. (c) Marangoni, B. A., and D'Agati, V. C.: Hepatorenal Failure in the Waterhouse-Friderichsen Syndrome: Clinical-Pathologic Observations in Two Cases with Prolonged Survival Periods, *Am. J. M. Sc.* **207**:385, 1944. (d) Park, F. R., and Taplin, G. V.: Meningococcic Meningitis with Waterhouse-Friderichsen Syndrome: Report of Case with Recovery, Manuscript, Technical Information Division, Office of The Surgeon General. (e) Felder, S. L., and Stacy, A.: Meningococcemia with Waterhouse-Friderichsen Syndrome, Manuscript, Technical Information Division, Office of The Surgeon General. (f) Leichter, J. W., and Fish, C. E.: The Waterhouse-Friderichsen Syndrome: Report of Case in Soldier, *Mil. Surgeon* **93**:77, 1943. (g) Bush, F. W., and Bailey, F. R.: The Treatment of Meningococcus Infections with Especial Reference to the Waterhouse-Friderichsen Syndrome, *Ann. Int. Med.* **20**:619, 1944. (h) Potter, H. W., and Bronstein, L. H.: The Waterhouse-Friderichsen Syndrome: Report of Case Terminating in Recovery, *J. Lab. & Clin. Med.* **29**:703, 1944. (i) Kinsman and others.<sup>7</sup> (j) Thomas.<sup>9</sup> (k) Bernhard and Jordon.<sup>12a</sup>

A classic instance of this condition follows:

CASE 11.—A 21 year old soldier began to suffer from headache, weakness, general aching and vomiting one and a half hours prior to his admission to the hospital at 5 p. m. on April 17, 1943. By midnight a temperature of 106 F., a purpuric eruption of the skin and an irrational mental state had developed. Because of obvious meningococcic bacteremia 4 Gm. of sodium sulfadiazine was given parenterally. By 5 a. m. on April 18 he was stuporous, cyanotic, cold and in collapse, with a pulse rate of 160 and a blood pressure of 70 systolic and 35 diastolic. In spite of large doses of sulfadiazine, adrenal cortex extract, dextrose, sodium chloride and plasma the purpuric rash spread and large areas of ecchymosis developed (fig. 4). Circulatory collapse increased, the pulse became imperceptible and the blood pressure fell to 40 systolic and 0 diastolic. Coma developed. The patient died in pulmonary edema thirty-six hours after his admission to the hospital and twenty-six hours after the institution of specific therapy. There had been no clinical evidence of meningitis, and his condition had been too critical to subject him to the strain of spinal puncture. The cerebrospinal fluid after death contained 2 cells and was sterile. Blood cultures during life contained meningococci, and many organisms were seen in leukocytes in smears of the peripheral blood and of purpuric lesions of the skin.

Chemical analyses of the blood revealed that nonprotein nitrogen was 75 mg., creatinine 1.7 mg., chlorides 478 mg., sugar 126 mg. and sulfadiazine 20 mg. per hundred cubic centimeters. Autopsy revealed massive hemorrhage in both adrenals and no evidence of meningitis (fig. 5).

An analysis of the degree of adrenal hemorrhage in relationship to the duration of life indicates that patients with massive hemorrhage die most rapidly. However, there is ample evidence that shock and circulatory collapse incident to fulminant sepsis may occur without adrenal hemorrhage. As has been stated, fulminant sepsis with no adrenal abnormality at autopsy (case 10) may produce a clinical picture identical with the classic Waterhouse-Friderichsen syndrome. Profound injury to other organs as a result of "toxemia" and widespread hemorrhage, frequently with pronounced cellular infiltration of the myocardium, may well be the sole cause of death. Marangoni and D'Agati,<sup>13c</sup> in a report on 2 patients with long survival periods (eighty and eighty-eight hours), have expressed the opinion that there are two distinct stages in the Waterhouse-Friderichsen syndrome. The first is the phase of profound shock and circulatory collapse. If this is survived, the second, a "hepatorenal" phase, begins. It is characterized clinically by considerable oliguria with azotemia and pathologically by severe central necrosis of the liver associated with changes in the glomeruli and tubules of the kidneys. A number of observers<sup>14</sup> stated the belief that circulatory collapse in the Waterhouse-Friderichsen syndrome is primarily the result of broadspread tissue changes and hemor-

14. Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura with Adrenal Hemorrhage in Adult (Waterhouse-Friderichsen Syndrome): Discussion of Role Played by the Adrenal Gland in the Production of the Syndrome, J. A. M. A. **125**:884 (July 29) 1944. Kinsman and others.<sup>7</sup> Thomas.<sup>9</sup> Wright and Report.<sup>13a</sup> Marangoni and D'Agati.<sup>13c</sup>

rhages rather than of adrenal insufficiency secondary to hemorrhage into these glands. It is pointed out<sup>15</sup> that (1) in this condition death requires but a few hours whereas adrenalectomized animals live for several days, (2) classic clinical manifestations of the Waterhouse-Friderichsen syndrome may occur in patients with fulminant sepsis without there being abnormality of the adrenals at autopsy, (3) conversely, among the 126 patients found to have adrenal hemorrhage at autopsy in 5 the manifestations were not those of the Waterhouse-Friderichsen syndrome,<sup>8</sup> (4) some patients who recovered received no adrenal cortex hormone and (5) in patients who recovered the discontinuation of the use of adrenocortical hormone after a few days did not lead to a recurrence of symptoms. If adrenal insufficiency secondary to hemorrhagic destruction of the adrenals had been present, such temporary therapy would hardly have been curative.



Fig. 4.—Broadsread ecchymotic rash in a patient with fulminant bacteremia with peripheral vascular collapse and bilateral adrenal hemorrhage.

Prior to the development of sulfonamide compounds the Waterhouse-Friderichsen syndrome was invariably fatal. Weinberg and McGavack<sup>16</sup> in 1945 collected from the literature 11 instances of recovery and reported an additional 1. Thirteen other instances of recovery not included by these authors have been either reported among army personnel or observed by me.<sup>17</sup> There are undoubtedly a number of

15. Kinsman and others.<sup>7</sup> Wright and Reppert.<sup>13a</sup>

16. Weinberg, L. D., and McGavack, T. H.: Waterhouse-Friderichsen Syndrome: Report of Case with Recovery, *New England J. Med.* **232**:95, 1945.

17. Wechsler, H. F., and Rosenblum, A. H.: Meningococcic Meningitis, *Mil. Surgeon* **95**:132, 1944. Meyer, R. R.: Meningococcal Meningitis: A Report

(Footnote continued on next page)

additional cases which have not been reported. When recovery takes place there is no way of proving or disproving the presence of adrenal hemorrhage. It seems likely that some of the patients who recovered actually had fulminant sepsis without adrenal hemorrhage though clinically exhibiting the Waterhouse-Friderichsen syndrome.

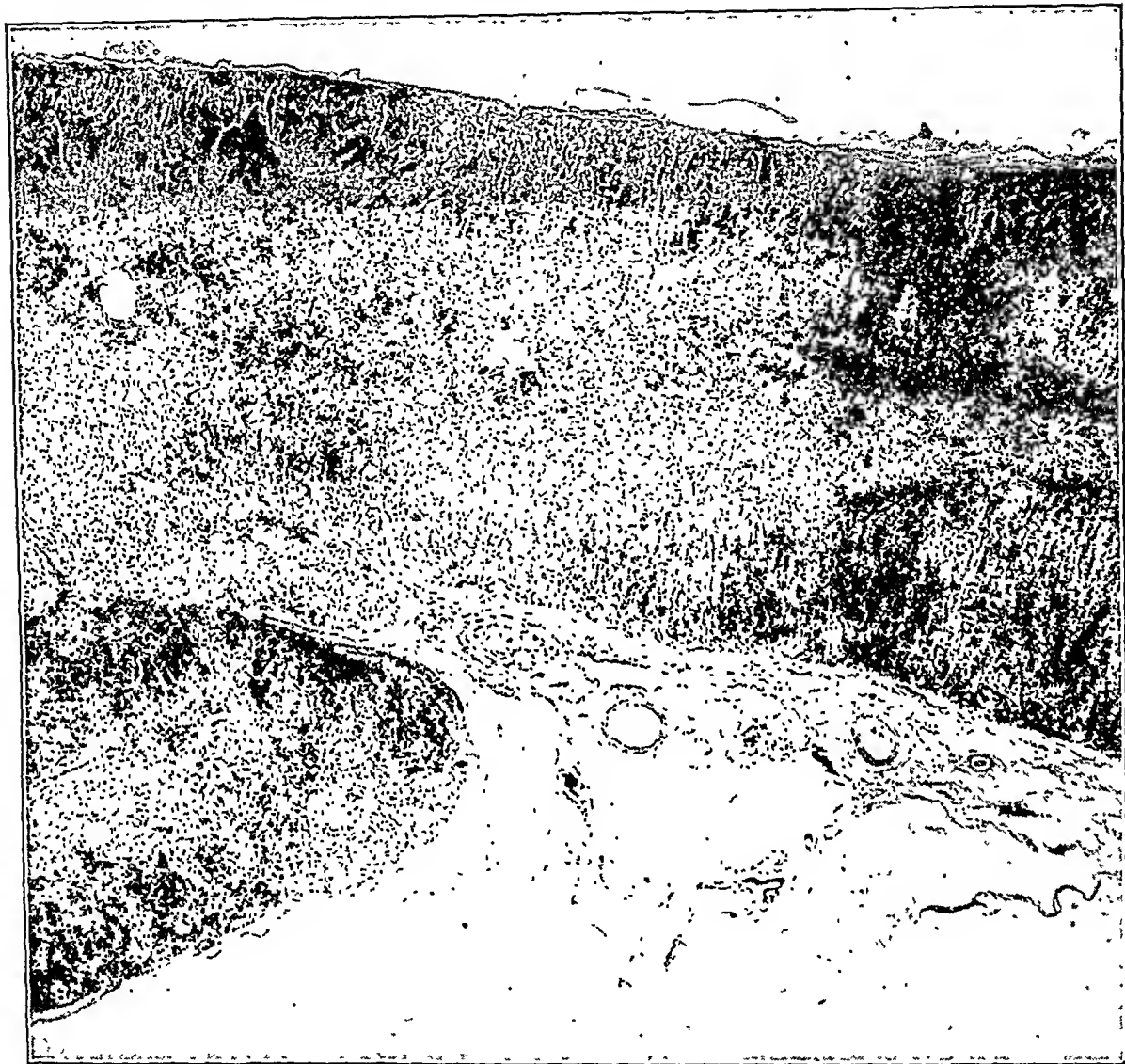


Fig. 5.—Photomicrograph of massive hemorrhage into adrenal in a patient with fulminant bacteremia with peripheral vascular failure;  $\times 15$ . (U. S. Army Medical Museum negative no. 72796.)

It seems wise to emphasize again that in only 56 per cent of a group of 32 patients with meningococcemia uncomplicated by meningitis was the diagnosis confirmed by the presence of organisms in the blood

of Thirty-Three Cases with No Deaths, *New England J. Med.* **230**:452, 1944. Marangoni, B. A., and D'Agati, V. C.: The Waterhouse-Friderichsen Syndrome, *ibid.* **231**:1, 1945. Kinsman and others.<sup>7</sup> Wright and Reppert.<sup>13a</sup> Park and Taplin.<sup>13d</sup> Felder and Stacy.<sup>13e</sup> Bush and Bailey.<sup>13g</sup> Potter and Bronstein.<sup>13h</sup>

culture.<sup>4</sup> This illustrates a most important point. An accurate diagnosis of meningococcemia can and indeed must be made long before there is any report of the results of blood culture if one hopes to prevent the advent of meningitis or fulminant bacteremia. The clinical picture in most cases is sufficiently clear to permit a positive diagnosis. If sulfadiazine is started as soon as the diagnosis is made and one blood sample taken for culture, meningitis or fulminant bacteremia may be prevented and recovery expected. If therapy is delayed and repeated blood samples taken for culture, the number of cases confirmed bacteriologically is higher but the number of cases of meningitis is markedly increased, with resultant higher mortality.

#### TREATMENT

*Acute or Chronic Bacteremia.*—Four grams of sulfadiazine was given by mouth, followed by 1.0 Gm. every four hours until fever, symptoms and other manifestations of infection had been absent for at least forty-eight hours. Parenteral administration of comparable amounts of sulfadiazine in dilute solution was used in the presence of vomiting. This dosage was usually sufficient to maintain a blood concentration of from 5 to 11 mg. per hundred cubic centimeters and as a rule prevented the development of fulminant bacteremia or meningitis.

*Fulminant Bacteremia with Peripheral Circulatory Failure.*—This was a major medical emergency and required immediate action and continued constant observation by a resourceful physician. Two physicians were advantageously employed in carrying out the early treatment. A good nurse who was thoroughly familiar with the ward and the hospital was essential. Even though meningitis was present or suspected, it was of secondary importance and the patient was not subjected to the strain of lumbar puncture. Sodium sulfadiazine (0.1 Gm. per kilogram of body weight dissolved in a liter of 5 per cent dextrose in isotonic solution of sodium chloride) was started intravenously while in the other arm 50,000 units of penicillin was administered by syringe in 20 cc. of isotonic solution of sodium chloride or distilled water. Through the same needle 30 cc. of aqueous extract of adrenal cortex was given and 20 cc. given intramuscularly or intravenously as often as every two hours if indicated. Forty thousand units of penicillin was given intramuscularly at the same time as the first intravenous dose, and this was continued every two hours as long as necessary. If peripheral circulatory failure was marked, all penicillin was given intravenously. When the penicillin had been given intravenously, 500 cc. of plasma was given through the same needle. Sodium sulfadiazine (0.05 Gm. per kilogram of body weight in 500 cc. of 5 per cent dextrose in isotonic solution of sodium chloride) was administered intravenously after four hours. Subsequent dosage was determined by frequent esti-

mations of blood concentration, as fluctuations in fluid balance occurred and urinary output was generally low. The blood concentration was maintained at between 15 to 20 mg. per hundred cubic centimeters. Oxygen by tent, nasal catheter or Boothby-Lovelace mask was given continuously to combat cyanosis, and external warmth of moderate degree was applied to the body.

The fluid intake was maintained at from 3 to 4 liters per day, but because of the danger of pulmonary edema isotonic sodium chloride was not given in excess of 1 liter daily after the first twenty-four hours. A liter of fluid was usually given as sixth-molar sodium lactate and another as 5 or 10 per cent solution of dextrose. Plasma in quantities of 500 cc. was used as indicated if the blood pressure remained low. During such a regimen, careful observation was maintained in order to recognize the early evidences of threatening pulmonary edema. Sedatives may be necessary during the early phase as the patients are frequently lucid and extremely restless. Paraldehyde is an excellent sedative, but morphine in small doses was usually needed.

For patients with fulminant bacteremia in whom the manifestations were not those of shock, plasma, oxygen and aqueous adrenal cortex extract were omitted. Though the evidence is against adrenal insufficiency as a cause for shock, few have been willing to discard the use of adrenal cortex extract.

Penicillin, though a most effective drug in the treatment of meningococcic bacteremia, has the disadvantage of entering the cerebrospinal fluid in only small and unpredictable quantities.<sup>18</sup> Since meningitis is a common sequel of bacteremia and may be present in the absence of meningeal signs, sulfadiazine is the drug of choice. This material rapidly enters the spinal fluid in high concentrations, where its bacteriostatic qualities may prevent meningitis or may affect its course beneficially if it is already present. Penicillin should be retained for use in conjunction with sulfadiazine in fulminant bacteremia and for replacement when there is intolerance to this drug or if complications from it develop. In the rare instances of failure or inadequate response to sulfadiazine penicillin should be given.

#### SUMMARY

During outbreaks of meningococcic infection, bacteremia without involvement of the meninges is common. It is essential that the physician be able to recognize the disease in its various forms prior to the report of the blood culture so that prompt treatment may be instituted. The various clinical forms observed in soldiers during World War II have been described. Sulfadiazine has proved to be the drug of choice.

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18. Kinsman, J. M., and others: The Penetration of Penicillin Through the Normal and Inflamed Membranes, *New England J. Med.*, to be published.

## REGULATION OF PULMONARY ARTERIAL BLOOD PRESSURE

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STOCKHOLM, SWEDEN

SINCE Hering's discovery,<sup>1</sup> about twenty years ago, that increased pressure in the carotid sinus reflexly produces bradycardia and arterial hypotension, a great deal of work has been done in the regulation of systemic arterial blood pressure. It has been proved, especially by the work of Heymans and his associates,<sup>1a</sup> that the sinus and aortic regions are of paramount importance in this connection; on the one hand, increased arterial pressure stimulates pressosensitive endings of the sinus and aortic nerves and provokes inhibition of the cardiac and vasomotor centers, and, on the other hand, the lowering of the oxygen and the rise of the carbon dioxide tension in the arterial blood stimulate chemoreceptors and from them, by way of a reflex, also the centers mentioned. Having been for some time engaged in studies on these questions it appeared to my colleague, Professor von Euler, and me<sup>2</sup> that it might be worth while to investigate whether similar arrangements could be demonstrated in the lesser circulation. I would like to present a résumé of the results obtained by us as well as by Logaras,<sup>3</sup> who has been working in my laboratory.

Of course, we realized that the situation is different for the two systems. The lungs, being placed in series with the general circulation, would scarcely be dependent on the maintenance of a certain pressure level in the pulmonary artery in order to ensure the blood supply to the organ itself, corresponding to the situation with regard to a number of organs in the general circulation, notably the central nervous system and the kidneys. There would seem, however, to be reason for some regulation in so far as a high level of pulmonary blood pressure

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Read before the Section on Pathology and Physiology at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1947.

1. Hering, H. E.: *Die Karotissinusreflexe auf Herz und Gefäße vom normal-physiologischen, pathologisch-physiologischen und klinischen Standpunkt*, Dresden, Theodor Steinkopf, 1927.

1a. Heymans, C.; Bouckaert, J. J., and Regniers, P.: *Le sinus carotidien et la zone homologue cardio-aortique*, Paris, Gaston Doin & Cie, 1933.

2. von Euler, U. S., and Liljestrand, G.: *Acta physiol. Scandinav.* **12**:301, 1946.

3. Logaras, G.: *Acta physiol. Scandinav.* **14**:120, 1947.

might be harmful, on account of the risk of pulmonary edema, and demands might also arise connected with the special function of the lungs.

In our experiments anesthetized cats were used. A special cannula was inserted in the pulmonary artery in such a way that the wall was gripped between two flanges (fig. 1) and connected with a vertical glass tube and a piston recorder. Sometimes the pressure from the left auricle was measured in a similar way. The thorax being closed carefully at an inflated state of the lungs, spontaneous respiration could, as a rule, be established; in some cases artificial respiration was used.

Indications of a nervous influence on the pulmonary arterial pressure were obtained in some instances. Thus, the pressure gradient from the pulmonary artery to the left auricle rose about 30 per cent after the administration of small doses of epinephrine (0.005 to 0.02 mg.) and up to several hundred per cent after the administration of 0.3 mg. of

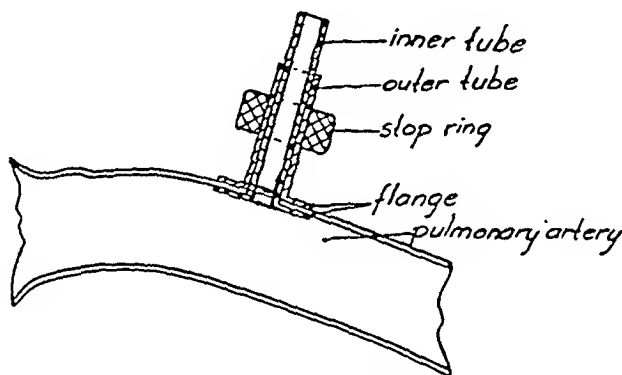


Fig. 1.—Drawing of a cross section of the cannula used.

ergotamine. It might be argued that this was the result of passive distention. But if the artery to the left lung was occluded, thereby greatly increasing the flow of blood through the remaining vascular bed, a rise in the pulmonary arterial pressure of only 20 to 30 per cent (fig. 2) was obtained. It therefore seems necessary to assume that the drugs mentioned exert a direct influence on the vessels. In 1 experiment (fig. 3), large waves appeared in the pulmonary arterial pressure with only small variations in the systemic arterial pressure. Since, on the other hand, clamping of the carotid arteries resulted in the usual increase in the systemic pressure with only a slight rise in the pulmonary arterial pressure (fig. 4), it seems reasonable to assume that the effect just mentioned is the result of rhythmic activity in the vasomotor center.

Our efforts to demonstrate an influence on the pulmonary arterial pressure through nervous mechanisms operating under physiologic conditions were not successful, however. The small rise obtained after clamping the carotids might be explained as secondary, and the increase after occlusion of the artery to the left lung can easily be explained by



the great distensibility of the vessels. Neither vagotomy nor the administration of ergotamine had any influence on the result. If the general flow of blood was increased by about 200 to 300 per cent, by electrically induced muscular work, the pulmonary arterial pressure rose in a similar way, as after the left pulmonary artery was clamped, and this result was unaffected by vagotomy.

Turning our attention to the possibilities of obtaining results with chemical stimulants, we tried using different concentrations of carbon dioxide and oxygen. Carbon dioxide induced a small, or under special conditions a moderate, increase in the pressure (fig. 5). This effect remained after vagotomy, but could be abolished or even reversed by

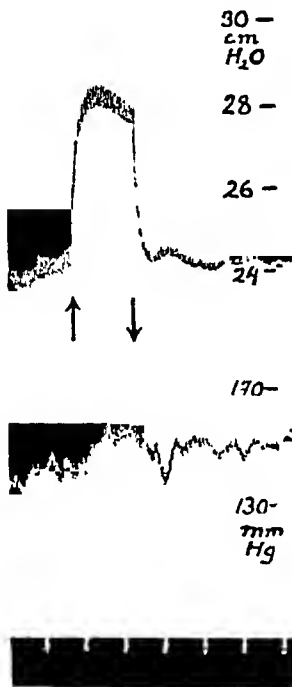


Figure 2

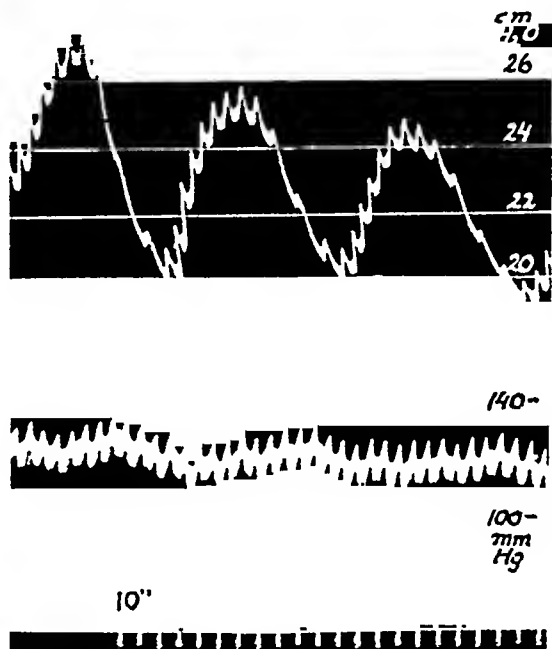


Figure 3

Fig. 2 (cat weighing 3.0 Kg., anesthetized with chloralose).—The upper curve represents pulmonary arterial pressure and the lower curve systemic blood pressure. The arrows indicate occlusion and opening of the left pulmonary artery. Artificial respiration was employed, with an open thorax (time, thirty seconds).

Fig. 3 (cat weighing 2.9 Kg., anesthetized with chloralose).—The upper curve represents pulmonary arterial pressure, with spontaneous waves; the lower curve records systemic blood pressure. The recording was made with spontaneous breathing and a closed thorax (time, ten seconds).

administration of ergotamine. Definite and somewhat unexpected results were obtained with variations in oxygen pressure. Oxygen want led to a rise in pulmonary arterial pressure (fig. 5), and oxygen inhalation from air resulted in a definite drop. Figure 6 demonstrates that during inhalation of air and oxygen the levels of pressure are different and that the increase during muscular work is added to these levels, the increase

when breathing oxygen being somewhat less. Since the effect of alteration in the oxygen pressure seems to be of certain importance, I will dwell a little further on it.

In numerous experiments these effects have been observed rather regularly. There are variations in individual susceptibility, however. Figure 7 gives an illustration of significant effects of oxygen want. In figure 7 *A*, a large rise in the pulmonary arterial pressure is caused by a reduction of the oxygen content from air to 15 per cent oxygen in nitrogen. Of course, it is possible that in this case the rise in the pulmonary arterial pressure might, to some extent, have been due to back pressure from the left auricle, if the function of the heart had been impaired.

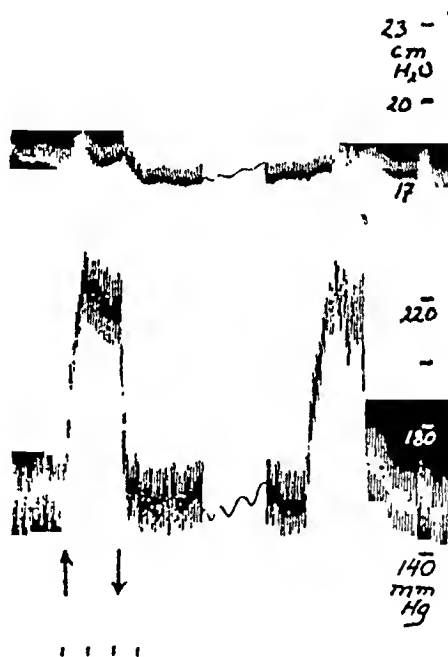


Fig. 4 (cat weighing 3.5 Kg., anesthetized with chloralose).—The upper curve represents pulmonary arterial pressure and the lower curve systemic pressure. The arrows indicate occlusion and opening of the common carotid artery. The recording was made with spontaneous breathing and a closed thorax (time, thirty seconds).

From figure 7 *B*, however, it can be seen that a decided effect on the pulmonary arterial pressure may be obtained from oxygen want, without impairment of the function of the heart. In this case—possibly with somewhat insufficient spontaneous respiration—even the shift from oxygen to air led to a rise in the pulmonary arterial pressure from 25 to 65 cm. of water, thus a rise of 160 per cent. The interesting point is that the pressure in the left auricle was hardly affected at all. From figure 8 it can be seen that the fall in the pulmonary arterial pressure is less for 50 per cent oxygen than for pure oxygen, the drop being from 21 to 19 cm. and from 23 to 19 cm., respectively. A small increase in the pressure

of the left auricle was observed, probably due to a sudden increase of the inflow when the vessels of the lungs became dilated.

The effect of oxygen or oxygen want on the pulmonary arterial pressure can be explained only as caused by variations in the degree of contraction of the arterioles and precapillaries of the lungs. There is obviously no back pressure, and it is improbable that such enormous variations in the general flow of blood should occur, as must be assumed, if a passive distention should be responsible for the effect. There must be some special mechanism by the aid of which the oxygen tension in the lungs influences the degree of contraction of the arterioles and the

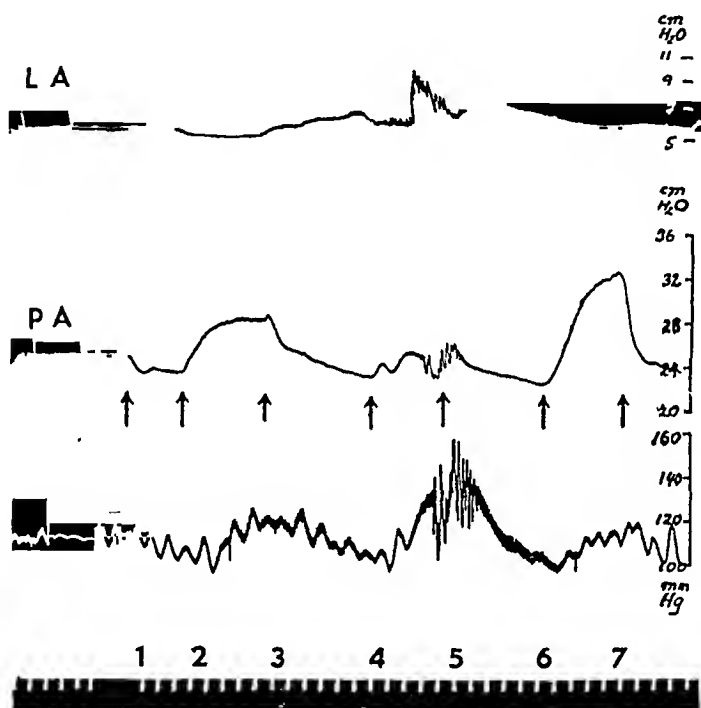


Fig. 5 (cat weighing 3.9 Kg., anesthetized with chloralose).—The uppermost curve represents pressure in the left auricle; the middle curve represents pulmonary arterial pressure, and the lower curve represents systemic blood pressure. At point 1, oxygen from air was administered, at 2, 6.5 per cent of carbon dioxide in oxygen; at 3, oxygen; at 4, 18.7 per cent of carbon dioxide in oxygen; at 5, oxygen; at 6, 10.5 per cent of oxygen in nitrogen and at 7, oxygen. Artificial respiration was employed with an open thorax (time, thirty seconds).

precapillaries. With regard to this mechanism, we have observed that the effect is not abolished by vagotomy or extirpation of the stellate ganglions or by the administration of ergotamine, dihydroergotamine, atropine or yohimbine. It is thus a local effect, and it would seem possible that it is called forth by the degree of oxygenation of the venous blood in the arterioles of the lungs, though this point must, of course, be investigated thoroughly.

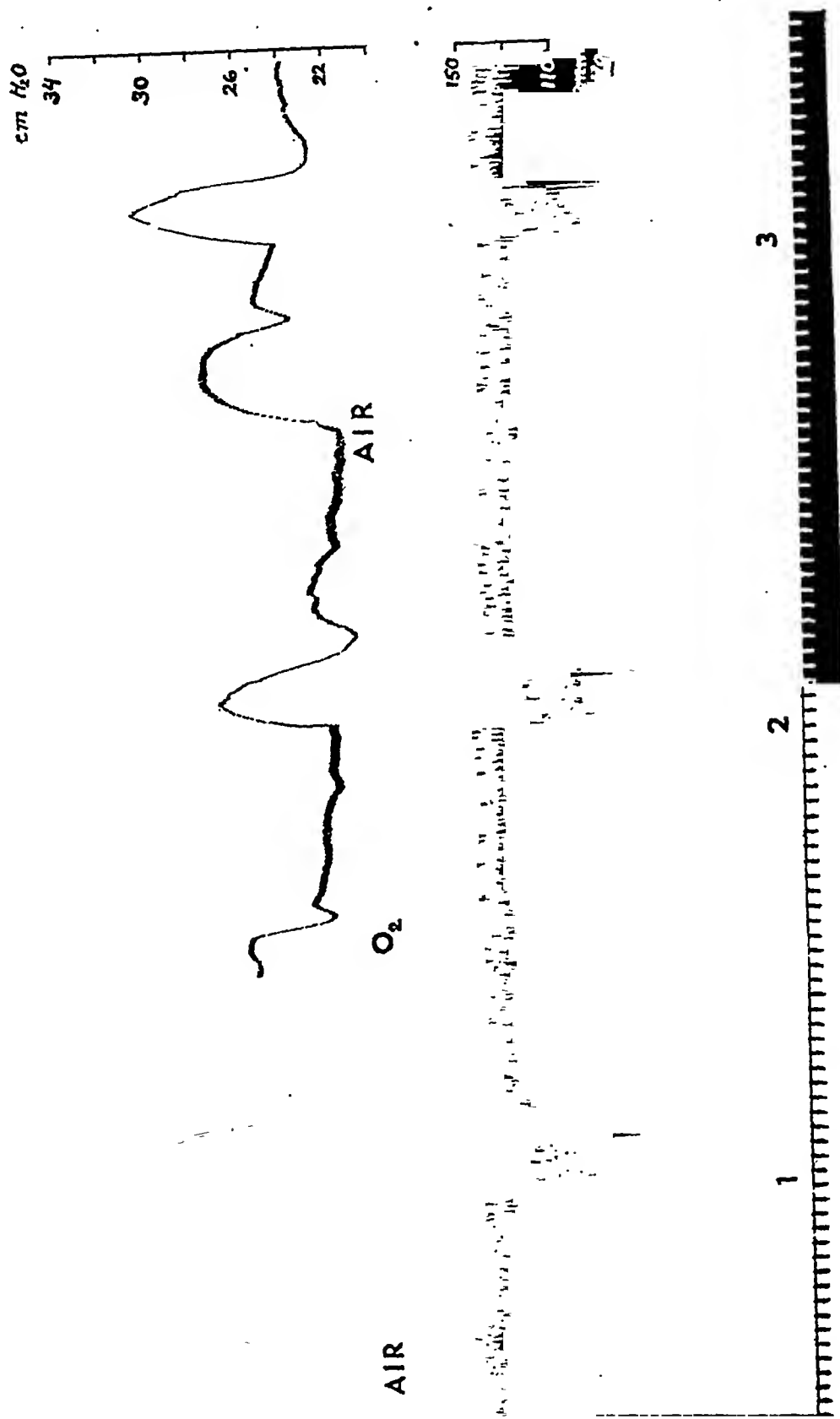


Fig. 6 (cat weighing 4.1 Kg., anesthetized with chloralose).—The upper curve represents pulmonary arterial pressure and the lower curve systemic blood pressure.

Increase of carbon dioxide and decrease of oxygen pressure act in the same direction, both raising the pulmonary arterial pressure. The effect of oxygen want is much stronger, however, and will be the main effective factor when the respiratory air is simultaneously enriched in carbon dioxide and reduced in oxygen content. This is borne out by the experiment reproduced in figure 9. The animal was made to breathe through a tube, the part nearest to the trachea being at first filled with coarse sand and in another trial, a few minutes later, with soda lime. The extra dead space in both instances was therefore the same, the only difference being that in the first instance carbon dioxide accumulation took place simultaneously with the decrease in oxygen percentage. As seen from the figure, the rise in pressure is the same in both instances.

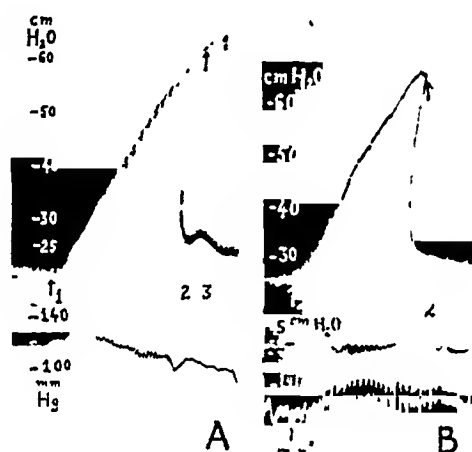


Fig. 7.—*A* (cat weighing 2.3 Kg., anesthetized with chloralose); the upper curve represents pulmonary arterial pressure, and the lower curve represents systemic blood pressure. At point 1, 15 per cent of oxygen in nitrogen (from air) was administered; at point 2, air was breathed and at 3, oxygen. Artificial respiration was used (time, thirty seconds). *B* (cat weighing 3.8 Kg., anesthetized with chloralose); the upper curve represents pulmonary blood pressure, the middle curve left auricular pressure and the lower curve systemic blood pressure. At point 1, air (from pure oxygen) was breathed, and at point 2, oxygen was used. Spontaneous breathing was employed (time, ten seconds).

If the inspiratory or expiratory resistance was increased, a rise in the pulmonary arterial pressure resulted. With regard to the expiratory resistance, it was observed (fig. 10) that the effect was to a considerable extent due to oxygen want, since breathing of oxygen greatly reduced the expiratory resistance. An increase of the pressure in the lungs during the whole respiratory cycle, obtained by placing a suitable weight on the gas bag and adjusting it so that the gas was slowly driven through the Müller valves, did not influence the pulmonary arterial pressure, a result of some interest with regard to the modern application of oxygen under positive pressure as a therapeutic agent.

The ultimate purpose of any regulation of the blood pressure is to maintain an adequate flow of blood to the organs of the body, and this is achieved in different ways within the systemic and the pulmonary circulations. The results obtained have confirmed the generally accepted view that the pulmonary arterial blood pressure is not integrated and held at a relatively constant level to the same extent as the systemic pressure. If a corresponding mechanism exists for the pulmonary system—and this can by no means be excluded—it must be rather poorly developed. On the other hand, a special mechanism has been found in the lungs, by the aid of which the degree of contraction of the arterioles can be regulated. The main agent in this regulation is the oxygen pressure; to some limited extent the carbon dioxide pressure may also contribute. The effect is presumably mediated through the venous blood in the arterioles of the lungs, thereby enabling a local action according to the needs in order to correlate breathing and circulation.

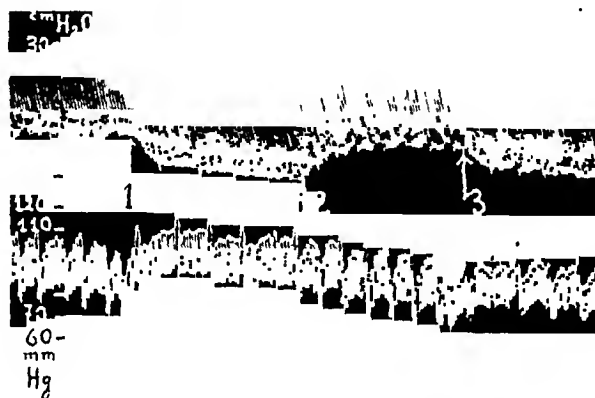


Fig. 8 (cat weighing 3.7 Kg., anesthetized with chloralose).—The upper curve represents pulmonary arterial pressure and the lower curve systemic blood pressure. At points 1, 2 and 3, the animal received oxygen (from air), air and 50 per cent of oxygen in nitrogen, respectively. The experiment was done with a closed thorax and spontaneous breathing (time, ten seconds).

It is clear that mechanical factors, e. g., variations in posture, will easily influence the flow of blood through the lungs. It has been emphasized especially by Sonne (1936) <sup>4</sup> that the different parts of the lungs are ventilated unevenly also in normal subjects, and from this he concluded that the composition of the alveolar air must vary greatly in the different parts of the lungs. This conclusion is based on the assumption, however, that the flow of blood through the lungs remains constant in spite of variations in the relative ventilation. From our experiments it is obvious that this is not the case. As soon as a steady state has been attained the flow of blood will, to a certain extent, have become regulated according to the efficiency of aeration; it will become restricted where ventilation is poor but increased where it is good, and in this way a

<sup>4</sup> Sonne, C.: *Acta med. Scandinav.* 90:315, 1936.

strict economy will be upheld. We thus come to the conclusion that oxygen want, which is known to lead to vasodilatation in the systemic circulation, acts in the opposite way in the pulmonary circulation; in the former case "the call for oxygen" of the different organs will become satisfied, and in the latter case the flow of blood will be directed from parts of the lungs which are badly ventilated to parts where the purpose of the lesser circulation can be better fulfilled. It seems probable that the increased mean capacity of the lungs during oxygen want will also be of importance in this connection.

The results obtained also seem to be of interest from other points of view.

It has been shown by several observers (Clamann and Becker-Freyseng, 1939,<sup>5</sup> Comroe, Dripps, Dumke and Deming, 1945,<sup>6</sup> and Ohlsson, 1946<sup>7</sup>) that after inhalation of oxygen for hours the vital capacity is

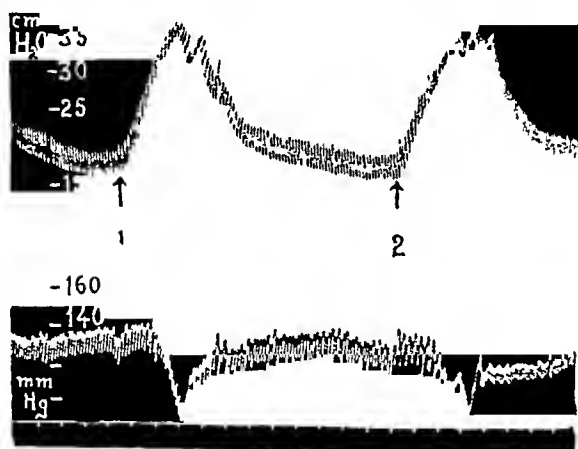


Fig. 9 (cat weighing 3.4 Kg.).—The upper curve represents pulmonary arterial pressure and the lower curve systemic blood pressure. At point 1, a rubber tube with a column of soda lime was interposed, and at point 2 the same tube with a column of sand (the particles of sand were the size of soda lime particles) was interposed. Spontaneous breathing was employed (time, thirty seconds).

decreased, usually 200 to 400 cc. It seems reasonable to assume that this is, in part at least, caused by the dilation of the vessels of the lungs. The experiments by Asmussen, Christensen and Sjöstrand (1939)<sup>8</sup> have shown that diminution of the vital capacity of this magnitude can easily

5. Clamann, H. G., and Becker-Freyseng, H.: *Luftfahrtmed.* 4:1, 1939.

6. Comroe, J. H., Jr.; Dripps, R. D.; Dumke, P. R., and Deming, M.: *Oxygen Toxicity: Effect of Inhalation of High Concentrations of Oxygen for Twenty-Four Hours on Normal Men at Sea Level and at Simulated Altitude of 18,000 Feet*, *J. A. M. A.* 128:710 (July 7) 1945.

7. Ohlsson, W.: *Nord. med.* 29:138, 1946.

8. Asmussen, E.; Christensen, E. H., and Sjöstrand, T.: *Skandinav. Arch. f. Physiol.* 82:193, 1939.

be obtained by pooling blood to the lungs. In my laboratory Alveryd and Brody (1947)<sup>9</sup> observed the decrease in the vital capacity after ten minutes of inhalation of oxygen, which is in agreement with the interpretation given.

The experiments also seem to shed some light on the mechanism of pulmonary edema. The theory of back pressure, once accepted in many quarters after the work of Welch (1878),<sup>10</sup> has met with adverse criticism, since in many cases the edema develops without any acute cardiac failure. Drinker<sup>11</sup> has set forth (1945) that the two fundamental factors causing transudation in the lungs are increased pulmonary capillary pressure and anoxia, and he pointed out that clinically they never work alone. Since anoxia has been observed to increase the arterial, and presumably also the precapillary, pressure in the lungs, the relation seems indeed an intimate one. Slowing of the circulation may well lead to some oxygen want without causing back pressure and may therefore be an important factor in the production of edema.

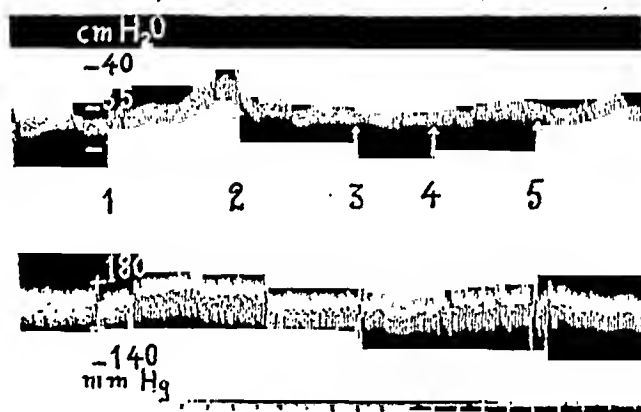


Fig. 10 (cat weighing 3.2 Kg.).—The upper curve represents pulmonary blood pressure and the lower curve systemic blood pressure. At point 1, there is an increase of the expiratory resistance by 1.5 cm. of water. At point 2, there is restoration of the expiratory resistance to normal. At point 3, there was breathing of oxygen. At point 4, there was increase of the respiratory resistance by 1.5 cm. of water. At point 5 there was restoration of the respiratory resistance to normal. Spontaneous respiration with a closed thorax was used (time, thirty seconds).

It is tempting also to try to explain some toxic effects of oxygen against the background outlined. As is well known, inhalation of 100 per cent oxygen at a pressure of 1 atmosphere and even less will lead to certain alterations in the lungs. Hyperemia is an early symptom, but edema and atelectasis will often develop if the inhalation continues for several hours. The lungs seem to be more easily affected by increased oxygen pressure than other organs, and this points to some local mechanism. It seems obvious that the hyperemia is simply the result of

9. Alveryd, A., and Brody, S.: *Acta physiol. Scandinav.*, to be published.

10. Welch, W. H.: *Virchows Arch. f. path. Anat.* 72:315, 1878.



the physiologic dilating effect of oxygen on the arterioles and precapillaries. The occurrence of edema after prolonged inhalation of oxygen would seem, however, to be in contrast to current opinions about the origin of this complication. Since oxygen will decrease the capillary blood pressure and abolish anoxia, how can it lead to edema? I would like to suggest the following answer. The lowering of the pressure and the disappearance of anoxia may certainly decrease the formation of lymph, but at the same time the greatly dilated blood vessels may constitute a mechanical obstacle for the removal of the fluid. The lymph vessels of the lungs take their origin around the alveolar ducts and will probably become more or less compressed by the widened arterioles and precapillaries. The balance between formation and removal of the lymph will thereby be disturbed, with edema as the result. It seems significant that edema can be prevented by interposing short periods of breathing of air; the improved draining might soon reestablish equilibrium, in spite of some increase in the formation of lymph.

Drinker,<sup>11</sup> after injection of a graphite suspension, observed a slow circulation in atelectatic parts of the lungs. This would seem to be the natural outcome of a local decrease in oxygen pressure and might act as protection, the complete absorption of the gases in the alveoli being delayed. Oxygen, however, acts in the reverse direction and is also itself more quickly absorbed than the gaseous mixture in the alveoli in oxygen want. The conditions will therefore be relatively favorable for the appearance of atelectasis when oxygen is breathed.

It is probable that the knowledge of the close correlation between oxygen pressure and the state of contraction of the pulmonary vessels will be of importance for the understanding of other pathophysiologic problems.

In conclusion, it may be emphasized that every addition to knowledge will reveal its value in the possibilities for explaining phenomena that have previously been obscure. It is a special value of experimental science that the results can often be applied to practical medicine, verifying the words of Starling, "Physiology of today is the medicine of tomorrow."

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11. Drinker, C. K.: *Pulmonary Edema and Inflammation*, Harvard Monographs in Medicine and Public Health, no. 7, Cambridge, Mass., Harvard University Press, 1945.

# CARCINOMA OF THE PANCREAS

## Diagnostic Criteria

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THE PREOPERATIVE diagnosis of carcinoma of the pancreas remains a challenge in spite of the many excellent studies made since De Costa's article in 1857. In this paper 90 cases are reviewed and compared with those in other studies<sup>1</sup> in the hope that earlier recognition of the disease may be accomplished.

## PATHOLOGIC FEATURES

In 85 of our cases the diagnosis was confirmed by operation and usually corroborated by biopsy, and in some instances it was also confirmed at autopsy. For 5 patients not subjected to operation the diagnosis was confirmed at autopsy. In a few cases it is not absolutely certain whether the primary lesion was precisely pancreatic or ampullar, but in all involvement of pancreatic tissue was clear.

The anatomic location of the lesion in this series is shown in table 1. As would be expected, the head of the pancreas was usually involved in patients with jaundice. Invasion of the body and tail was frequent in patients with jaundice and pain and in the majority of those without jaundice. The tumors were usually of the hard and scirrhus type, either ductal or acinar in origin. Differentiation from chronic pancreatitis was often difficult even at operation; biopsy was necessary for certain diagnosis. Metastasis was most frequent to the liver and the regional lymph nodes, although the duodenum, stomach, omentum, mesentery, adrenals, peritoneum, jejunum, mesocolon, abdominal wall, kidneys, lungs and pleura were involved in some cases; invasion of the superior mesenteric, portal, colic, splenic and gastrohepatic vessels was more or less frequent.

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

1. (a) Kiefer, E. D., and Moravec, M.: The Diagnosis of Carcinoma of the Pancreas, *S. Clin. North America* **23**:738, 1943. (b) Friedenwald, J., and Morrison, T. H.: Primary Carcinoma of the Pancreas: Clinical Observations, *Rev. Gastroenterol.* **8**:400, 1941. (c) Berk, J. E.: Diagnosis of Carcinoma of the Pancreas, *Arch. Int. Med.* **68**:525 (Sept.) 1941.

## AGE AND SEX

The average age of the patients on their admission to the hospital was 55.9 years, the youngest being 29 and the oldest 79. This is identical with the average age of 56 years reported by twelve previous authors.<sup>1c</sup> The sex ratio was 2 men to 1 woman; in 1,120 cases reported by twenty-one authors<sup>1c</sup> the sex ratio was 10 to 4.

## SYMPTOMS AND SIGNS

In the first modern review of carcinoma of the pancreas Bard and Pic in 1888<sup>2</sup> emphasized four points: jaundice, distention of the gall-bladder, cachexia and loss of weight. These concepts were popularly identified with the disease for a long time, although the literature since then has stressed the significance of pain rather than that of jaundice. By far the predominant chief complaint in our cases was pain, followed in frequency by jaundice, loss of weight, anorexia,

TABLE 1.—*Location of Carcinoma*

Anatomic Site	Jaundiced Patients	Nonjaundiced Patients	Total
Head.....	40	4	44
Head and body.....	0	1	1
Entire organ.....	3	3	6
Body only.....	6	6	12
Body and tail.....	2	5	7
Tail only.....	1	2	3
Not specified.....	8	9	17
Total.....	60	30	90

constipation, nausea and vomiting. The average duration of symptoms prior to admission to the hospital was 4.7 months, with a range of from one to twelve months.

*Pain.*—Pain was present in some form or other in all 30 of the cases in which there was no jaundice and in 45 of the 60 in which jaundice was present. The pain was typically gradual in onset and variable in location and quality, usually being steady and continuous, although in some cases it was intermittent, with an increase in frequency and severity as the weeks passed. In some instances the pain was colicky, boring or stabbing. Occasionally it was described as a burning pain; usually it was not related to meals. At times it was more severe when the patient was in the supine position, and like most pain it was worse at night. The most frequent sites were the epigastrium, the upper abdominal quadrants and the back (table 2); radiation to the back occurred in 22 cases and radiation to the left shoulder in 4. The

2. Bard, L., and Pic, A.: Contribution à l'étude clinique et anatomo-pathologique du cancer primitif du pancréas, Rev. de méd., Paris 8:257-282 and 363-405, 1888.

burning epigastric pain after meals suggested peptic ulcer, the colicky pains located under the right costal margin simulated gallbladder colic and the severe pains radiating to the back suggested the presence of pancreatitis. Salicylates afforded striking temporary relief to a few patients.

*Jaundice.*—Jaundice was present in 60 of the 90 cases (66.6 per cent) and was painless in 15. Of 1,206 cases reported by seventeen authors,<sup>1c</sup> jaundice was noted in 68.5 per cent. As a rule the jaundice was pronounced and progressive, although, as many writers have noted, remissions may occur. In 1 of our cases the jaundice subsided completely and the palpability of the gallbladder disappeared.

TABLE 2.—*Location of Pain (Primary)*

	Without Jaundice	With Jaundice	Total Patients
Epigastrium.....	14	23	37
Right upper quadrant.....	4	10	14
Back.....	5	9	14
Left upper quadrant.....	8	2	5
Left shoulder.....	1	1	2
Girdle pain.....	1	0	1
Abdomen (generalized).....	6	15	21

TABLE 3.—*Symptomatology Other Than Pain and Jaundice*

	Without Jaundice	With Jaundice	Total Patients
Loss of weight.....	23	49	72
Anorexia.....	12	24	36
Constipation.....	16	13	29
Nausea and vomiting.....	4	20	24
Diarrhea.....	7	11	18
Weakness.....	5	11	16
Dyspeptic complaints.....	4	11	15
Insomnia.....	1	5	6
Polydipsia and polyuria.....	0	4	4
Tarry stools.....	0	4	4
Ankle edema.....	2	2	4

*Loss of Weight.*—Loss of weight was recorded in 72 of the 90 cases and seemed to have been present in all; it was usually severe, averaging 32 pounds (14.5 Kg.), and it was accompanied with increasing cachexia (table 3).

*Anorexia.*—Anorexia is usually among the earliest symptoms and by itself may be significant even though it was cited as a symptom in only 36 of the 90 patients.

*Nausea and Vomiting.*—Nausea and vomiting were noted in 24 cases, due presumably to invasion of the bowel and to duodenal obstruction. It occurred in 20 of the 60 patients with jaundice and in 4 of the 30 without jaundice.

*Diarrhea.*—Diarrhea, noted in 18 cases, was often a puzzling manifestation. Steatorrhea was uncommon. The diarrhea was usually

accompanied not with cramplike intermittent pain but rather with the steady and continuous pain more typical of pancreatic neoplasm. Unexplained persistent diarrhea with abdominal pain and loss of weight should suggest the possibility of pancreatic disease.

*Signs.*—The gallbladder was palpated preoperatively in 52 per cent of the jaundiced patients. Ability to feel the gallbladder with reasonable certainty may be complicated by abdominal rigidity or by the presence of an enlarged liver; the quadrate lobe may be confused with the gallbladder. The average rate of palpability of the gallbladder among patients with jaundice in studies made by five other authors<sup>1c</sup> was 50.9 per cent.

An epigastric mass was noted in 32.2 per cent. Because of the recognized difficulty in the palpation of pancreatic tumors due to their retroperitoneal location near the lower costal margin, Eusterman<sup>3</sup> has recommended the use of intravenously induced anesthesia to facilitate examination. Kiefer and Moravec<sup>1a</sup> made the interesting observation that not all pancreatic tumors are fixed and that not all gastric tumors are movable.

*Pancreatic Enzymes.*—Numerous attempts have been made to correlate carcinoma of the pancreas with disturbances of enzyme secretion and of blood levels. Noteworthy results in blood lipase studies have been reported by Comfort and Osterberg,<sup>4</sup> who found an increased level in 40 per cent of their cases, and by Johnson and Bockus,<sup>5</sup> who found an increase in 6 of 11 cases, or 55.5 per cent. In our series few determinations were made, and hence we are not able to appraise their significance.

Some investigators, including Comfort, Osterberg and Parker<sup>6</sup> and Bauman and Whipple,<sup>7</sup> have studied the external pancreatic secretions, using a double-lumened tube. Comfort and his co-workers found diminished enzyme secretions in carcinoma of the head of the pancreas,

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3. Eusterman, G. B., and Wilbur, D. L.: Primary Malignant Neoplasm of the Pancreas: A Clinical Study of Eighty-Eight Verified Cases Without Jaundice, *South. M. J.* **26**:875, 1933.

4. Comfort, M. W., and Osterberg, A. E.: The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of Pancreas, *Proc. Staff Meet., Mayo Clin.* **15**:427, 1940.

5. Johnson, T. A., and Bockus, H. L.: Diagnostic Significance of Determinations of Serum Lipase, *Arch. Int. Med.* **66**:62 (July) 1940.

6. Comfort, M. W.; Parker, R. L., and Osterberg, A. E.: Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen, *Am. J. Digest. Dis.* **6**:249, 1939.

7. Bauman, L., and Whipple, A. O.: The Diagnostic Value of Pancreatic Function Tests in Forty-Seven Treated Surgical Cases, *Am. J. M. Sc.* **207**:281, 1944.

carcinoma of the papilla of Vater and chronic atrophic pancreatitis with steatorrhea; normal values were obtained in cirrhosis of the liver, hepatitis, choledocholithiasis and stricture of the common duct. Bauman and Whipple found similar results and pointed out that the secretion may be normal also in carcinoma of the ampulla if an accessory duct of Santorini is present. We have not studied these methods.

Fatty, foamy stools may occur and are significant, but they are not common.

TABLE 4.—Incidence of Glycosuria

Authors	Year	Number of Cases	Number of Cases in Which Glycosuria Was Present	Per-centage
Berk .....	1941	33	8	24.2
Friedenwald and Morrison.....	1941	40	6	15
Kiefer and Moravec.....	1943	74	7	10
Average of fourteen authors (Berk).....	1893 to 1941	692	65	9.4
University of Chicago.....	1946	81	22	27.1

TABLE 5.—Dextrose Tolerance Curves

Patient	Age	Blood Sugar Levels (Mg./100 Ce.)					Evidence of		Glycosuria
		Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	Jaundice Present	Metastasis to Liver	
W. P.....	57	116	145	202	193	171	Yes	No	Transient
A. D.....	49	79	172	255*	261	...	No	Yes	Transient
D. H.....	65	97	162	232	246	...	Yes	No	Transient
E. C.....	63	89	149	...	161	144	No	Yes	Transient
Repeat test		89	162	...	182	162	....	....	.....
O. F.....	45	83	141	210	162	125	No	....	Transient
V. H.....	63	96	142	193	190	153	No	Yes	Transient
J. H.....	54	117	162	190	193	170	Yes	Yes	None
M. F.....	40	107	116	138	158	147	Yes	No	Transient
P. B.....	45	81	124	178	254	149	Yes	No	Transient
C. M.....	37	84	191	138	164	128	Yes	Yes	None
B. O.....	50	88	174	...	221	110	Yes	....	Frequent
E. D.....	57	99	159	215	168	84	No	No	None
A. G.....	49	95	...	124	307	187	Yes	No	Transient
A. W.....	50	92	138	165	172	116	Yes	Yes	None
E. S.....	56	114	195†	251‡	192§	79	No	Yes	Transient
L. B.....	54	83	187	227	238	171	Yes	No	Transient
G. L.....	58	89	150	...	124	...	Yes	No	None
G. C.....	66	71	120	99	78	...	Yes	....	None
O. T.....	67	72	181	...	101	...	Yes	Yes	None
J. O.....	43	181	237	254	338	250	No	....	Yes
M. C.....	64	127	199	251	264	180	Yes	No	Yes

\* One hour and fifteen minutes after fasting level.

† Forty-five minutes after fasting level.

‡ One hour and twenty minutes after fasting level.

§ Two hours and twenty-five minutes after fasting level.

*Carbohydrate Metabolism.*—The possible relationship between pancreatic carcinoma and abnormalities in carbohydrate metabolism has interested many workers. In 1893 Mirallié<sup>8</sup> found glycosuria in 13 of 50 cases, but subsequent investigators found it less frequently. According to the composite data of fourteen authors in nearly a half century from Mirallié to Berk<sup>10</sup> the incidence of glycosuria was 9.4

8. Mirallié, C.: Cancer primitif du pancréas, *Gaz. d. hôp.* 46:889, 1893.

per cent (table 4); Mirallie's figure was 26 per cent and Berk's 24.2 per cent. Marble<sup>9</sup> reported that carcinoma of the pancreas constituted 13 per cent of two hundred and fifty-six malignant processes occurring with diabetes mellitus; McKittrick and Root,<sup>10</sup> from a study of 37 cases, raised the figure to 32.4 per cent. These are certainly striking figures and represent an incidence far above that of any other neoplasm occurring in patients with glycosuria. In our series preoperative glycosuria, although often transitory, was found in 21 of 81 cases studied (27.1 per cent).

The incidence of hyperglycemia in 25 cases was 60 per cent; this figure has little significance since these cases were usually selected from the glycosuria group. The dextrose tolerance test is a better index

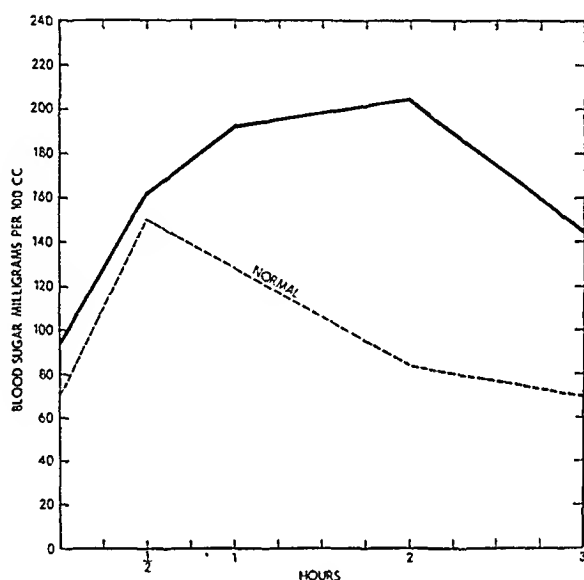


Fig. 1.—Composite dextrose tolerance curve of 21 patients treated.

of carbohydrate metabolism and is of particular interest. Berk<sup>10</sup> found the dextrose tolerance impaired in 7 of 9 and Friedenwald and Cullen<sup>11</sup> in all 4 of their cases. However Eusterman<sup>12</sup> in 1922 and Ransom<sup>13</sup> in 1938 found abnormalities in only 10.4 per cent and 17.1 per cent of their cases respectively. The tolerance curves obtained in 21 cases in this series are shown in table 5. It will be noted that the first 16

9. Marble, A.: Diabetes and Cancer, *New England J. Med.* **211**:339, 1934.

10. McKittrick, L. S., and Root, H. F.: *Diabetic Surgery*, Philadelphia, Lea & Febiger, 1928.

11. Friedenwald, J., and Cullen, T. S.: Carcinoma of the Pancreas: Clinical Observations, *Am. J. M. Sc.* **176**:31, 1928.

12. Eusterman, G. B.: Carcinoma of the Pancreas: A Clinical Study of One-Hundred and Thirty-Eight Cases, *Tr. Am. Gastro-Enterol. A.* **25**:126, 1922.

13. Ransom, H. K.: Carcinoma of the Pancreas and Extrahepatic Bile Ducts, *Am. J. Surg.* **40**:264, 1938.

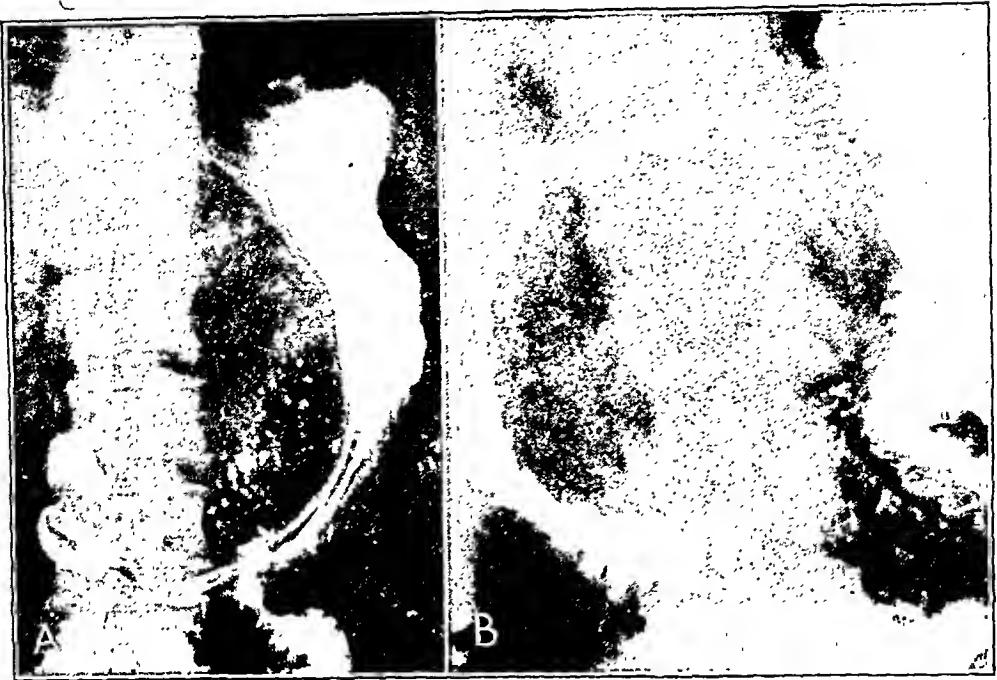


Fig. 2.—*A*, stomach curved about a large mass with distortion of the duodenum due to carcinoma of the body and tail. The patient, a 59 year old woman had a constant and "grinding" abdominal pain for eight months. A nontender fixed mass palpated in the mid-abdomen was diagnosed as a retroperitoneal mass, possibly a pancreatic cyst. *B*, wide duodenal loop in a 40 year old man who had symptoms of severe weight loss, anorexia and steady burning pain in the epigastrium. Laparotomy disclosed a large mass in the head of the pancreas. However the tip of the head was normal, thus perhaps explaining the absence of jaundice.

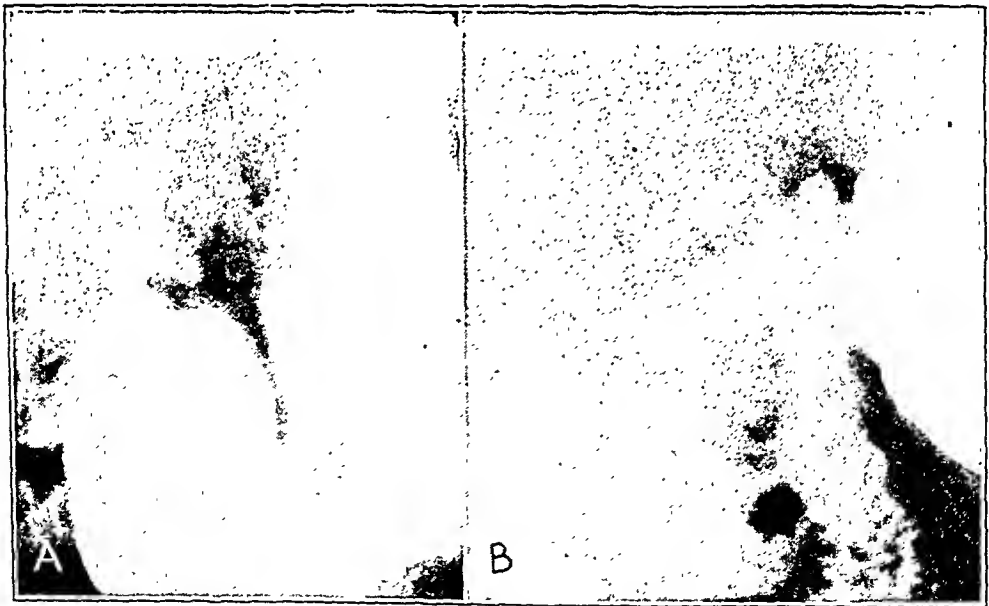


Fig. 3.—*A*, stenosis at apex of bulb with five hour gastric retention. Duodenal ulcer was suspected in this case, involving a 60 year old man who had symptoms of gastric retention and vomiting. Laparotomy revealed a hard stony pancreatic mass involving the second portion of the duodenum. *B*, high grade obstruction in a 76 year old man complaining of painless jaundice, weight loss, nausea and weakness. Exploration revealed a primary mass in the head of the pancreas encircling the duodenum.



patients had two hour intervals ranging from 151 to 307 mg. of sugar per hundred cubic centimeters of blood. According to the methods used in these tests, a normal two hour value would be 95 mg. per hundred cubic centimeters. In view of these notable and sustained increases, the first 16 patients have been arbitrarily classified as having the diabetic type of dextrose tolerance curves although none of them had more than occasional spilling of sugar in the urine and all had fasting blood sugar levels within or not far above normal ranges. Normal fasting blood sugar levels determined by these methods lie between 60 and 90 mg. per hundred cubic centimeters, all non-glucose-reducing substances being excluded. In cases 17, 18 and 19 the curves were

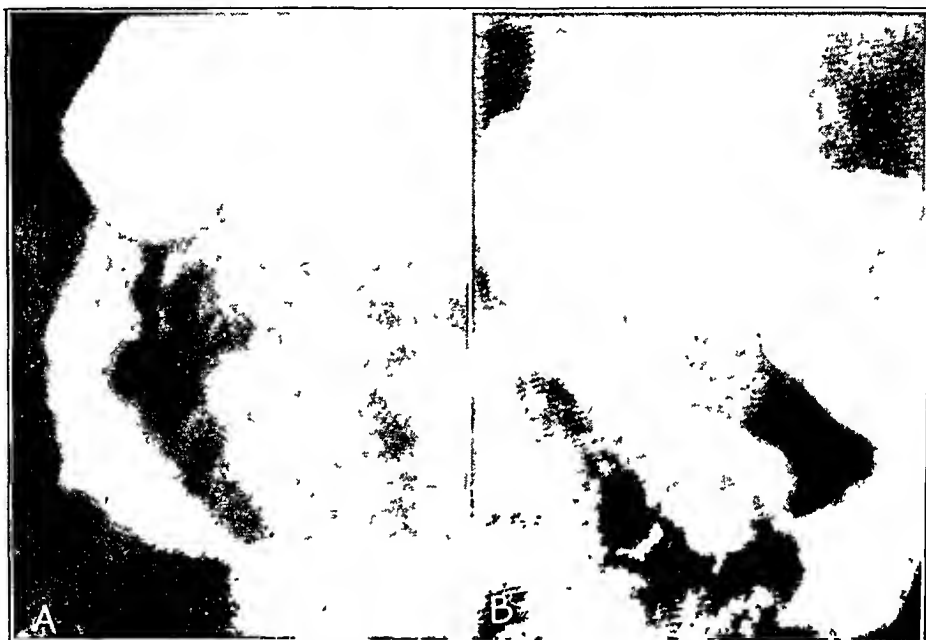


Fig. 4.—*A*, irregular destruction of the duodenal mucosa, with narrowing of the lumen from encroachment of carcinoma of the head of the pancreas in a 57 year old man who had jaundice, anorexia and a weight loss of 25 pounds (11 Kg.) in three months. The gallbladder was palpable. *B*, marked irregularity and narrowing of the second portion of the duodenum by invading carcinoma of the head of the pancreas in a 47 year old white man. On admission he complained of a dull aching pain in the right upper quadrant radiating to the back. Jaundice, itching, severe weight loss and a palpable gallbladder were present.

roughly within normal limits. The patients in cases 20 and 21 were considered to have diabetes mellitus because of definite persistent glycosuria and elevation of the fasting blood sugar level. The patient in case 20 required considerable doses of insulin. A composite curve for the 21 patients tested is shown in figure 1.

*Roentgenologic Examination.*—Notwithstanding the lack of a radio-paque dye which can be selectively absorbed by the pancreas, the indirect evidence afforded by careful roentgen examination greatly

enhances the chance of correct diagnosis. In this series evidence suggestive of the lesion was present in 35 (48.6 per cent) of 72 patients given such examination. The signs found most commonly were irregularities in the duodenal contour in 13 cases (18 per cent), distortion and displacement of the stomach in 10 cases (14 per cent), deformities of the duodenal bulb, sometimes with crater, in 9 cases (12.5 per cent) and expansion of the duodenal loop in 4 cases (5.6 per cent). Diverticulum of the second portion, observed in 4 patients, was not included among the positive findings. Figures 2 to 5 illustrate some of the roentgenograms suggesting the lesion found at operation. Lesions of the body and tail are less likely to produce roentgen signs

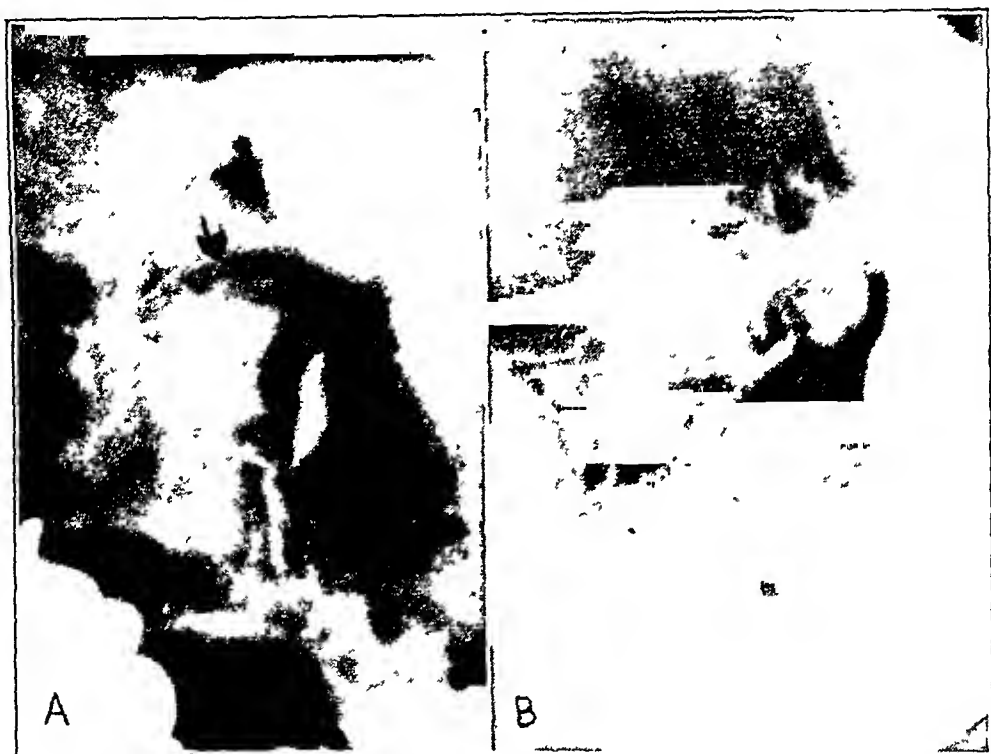


Fig. 5.—*A*, deformity of the second portion of the duodenum interpreted as due to neoplasm. The patient, aged 78, complained of pain in the lower right costal region. He was a chronic cardiac cripple with hypertension, auricular fibrillation and decompensation. Laparotomy revealed carcinomatous involvement of the head and uncinate process of the pancreas. *B*, stenosing lesion of the third portion of the duodenum in a 54 year old woman who had had epigastric pain, anorexia, vomiting and a weight loss of 25 pounds (11 Kg.) in five months. Pain radiated to the back and was worse at night. The primary lesion was carcinoma of the body of the pancreas invading the duodenum and the first part of the jejunum.

than those of the head, but they frequently distort the posterior wall of the body of the stomach or depress the stomach along the lesser curvature.

Cholecystograms disclosed nonvisualization of the gallbladder in 19 of 23 patients with jaundice and in 6 of 8 patients without jaundice. In only 2 instances was there a fully normal visualization: in 7 the roentgenograms disclosed stones.

## COMMENT

The first consideration in the diagnosis of carcinoma of the pancreas is to keep the disease in mind. This is easy when the patient presents the classic picture of jaundice, cachexia, loss of weight and a palpable gallbladder. Difficulty is encountered in regard to the patients without jaundice, who comprise one third of all those affected. Pain was present in all the patients studied. It was usually located in the upper part of the abdomen, though frequently in the back or radiating through to the back, and it was dull, steady and continuous in character and sometimes aggravated by the supine position. Rapid loss of weight was described in 72 of the 90 cases and seemed on physical examination to have been present in many more or perhaps in all. Constipation is a common symptom, but since it occurs in so many disturbances it is of little significance. Diarrhea is less frequent (20 per cent), but nevertheless it is an extremely important symptom for it tends to be persistent, not explained in the usual ways and not relieved by the usual measures. Steatorrhea is even more significant, and when coupled with the other symptoms mentioned it is almost pathognomonic. A transient glycosuria occurred in 27.1 per cent of cases; a diabetic type of dextrose tolerance curve was found in 18 of the 21 patients tested. Roentgenologic studies of the gastrointestinal tract serve to exclude lesions such as carcinoma of the stomach and may provide evidence of an extrinsic mass in the region of the pancreas. With more careful study and greater diagnostic acumen, the accuracy of pre-operative diagnosis should be greatly enhanced and patients subjected to operation at an earlier date.

## SUMMARY

1. Pain is an extremely important and early symptom of carcinoma of the pancreas; it was described in 83 per cent of the 90 cases studied. Although variable in character, it was typically dull and persistent and located high in the abdomen, but occasionally it was referred to the lower part of the abdomen. It was primary in the back in 14 cases and radiated to the back in 22 cases.
2. Jaundice was present in two thirds of the patients. In 58 per cent of these the gallbladder was palpated preoperatively.
3. An epigastric mass was noted in about one third of the patients.
4. Progressive and rapid loss of weight is extremely significant; it occurred in at least 80 per cent of our series. Persistent anorexia is of similar importance.
5. Persistent unexplained diarrhea, particularly steatorrhea occurring with abdominal pain, is suggestive of pancreatic neoplasm.
6. Glycosuria, usually inconstant, occurred in 27.1 per cent of the

cases; a diabetic type of dextrose tolerance curve was found in 18 of 21 patients tested. The diagnostic value of this procedure may be greater than it has been realized in the past.

7. Roentgen signs of diagnostic importance were noted in 48.6 per cent of the series. Greater attention should be paid to the possibilities of roentgen examination as a diagnostic procedure.

#### CONCLUSION

While there are no pathognomonic criteria for pancreatic neoplasm and the clinical picture is somewhat variable, the essential features are nevertheless so definite and the procedures mentioned so helpful that the diagnosis should be made earlier and more accurately than it is at present. The old injunction to "keep the disease in mind" cannot be repeated too often.

# ASSOCIATION OF SPONTANEOUS HYPOGLYCEMIA WITH HYPOCALCEMIA AND ELECTRO- CEREBRAL DYSFUNCTION

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**S**PONTANEOUS hypoglycemia, because of its varied symptomatology, can easily simulate a number of pathologic conditions, in particular epilepsy, narcolepsy, hysteria, psychoneurosis, hyperthyroidism, hypoparathyroidism, cardiac neurosis and angina-like symptoms.

While hypoglycemia simulating other diseases is now reported with rising frequency, little has been written on the coexistence of spontaneous hypoglycemia with other conditions of similar symptomatology. In this paper we should like to present observations on spontaneous hypoglycemia associated with electrocerebral dysfunction and hypocalcemia. Because of the similarity of the clinical picture in all three conditions the recognition of their coexistence appears to be of clinical importance.

## MATERIAL AND METHODS

A group of 8 patients presenting symptoms usually observed in psychoneurosis, spontaneous hypoglycemia or hypocalcemia were studied. The glucose tolerance tests were carried out by the routine oral method. The blood sugar contents were determined by the Folin-Wu method from samples of venous blood obtained while the patients were in the fasting state and at half hour intervals during the three hours following the ingestion of 100 Gm. of dextrose. The serum calcium content was determined by the Clark and Collip method.

Electroencephalograms were taken by means of the three channel Grass instrument. Both the bipolar and the monopolar system of recording potential variations from the brain were utilized. Electrodes were placed over the prefrontal, motor, parietal and occipital regions of the head bilaterally; indifferent electrodes were applied to the ear lobes.

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In order to avoid the effect of low blood sugar concentrations the electroencephalograms were taken after a normal meal (breakfast or lunch).

Patients were routinely hyperventilated for a period of two minutes after a preliminary resting record was obtained. The criteria for determining abnormal activity were the presence of slow potentials, high amplitude fast potentials and irregular or disorganized patterns.

#### REPORTS OF CASES

CASE 1.—A man aged 42 years, experienced a severe epigastric pain, with radiation into the right side of the chest, about two years prior to his first visit to the hospital. The pain came on two hours after dinner. The patient was given an injection of morphine, and then he was confined to bed for seven weeks, with the diagnosis of coronary thrombosis. Immediately after the attack and during his entire stay in the hospital he was free from pain and felt fairly well. Electrocardiograms taken on several occasions showed no evidence of cardiac disease. He remained well for the next two years until one morning when he found himself on the floor of his bathroom with no recollection of what had happened to him. From then on "blackouts," without loss of consciousness, occurred almost every day when he rose. They were accompanied with profuse perspiration, shortness of breath, a shaky feeling and a tendency to fall. On several occasions he had actual convulsions. The "blackouts" lasted a few minutes and were succeeded by "a feeling of being limp all over" for a period of hours. He was treated by many outstanding physicians and was given various medicines both orally and parenterally without effect. A neurologic check-up in a leading institution is reported to have been entirely noncontributory. Then psychotherapy was suggested but was refused by the patient.

Physical examination revealed nothing abnormal except for overweight and a slight tremor of the hands.

*Laboratory Data.*—A glucose tolerance test revealed spontaneous hypoglycemia (table 1). The blood sugar level, determined at the end of an attack which did not bring loss of consciousness and which lasted a few minutes, was 105 mg. per hundred cubic centimeters. The basal metabolic rate was —8 per cent. Liver function tests, cholecystography and drainage and culture of bile revealed no abnormalities. Roentgenologic examination of the gastrointestinal tract revealed a small hiatus hernia. The electroencephalogram was slightly abnormal as evidenced by random 6 to 8 cycles per second potentials, which were appreciably increased on hyperventilation. There was no evidence of a unilateral focus (figure).

The patient was placed on a maintenance diet for hypoglycemia and given diphenylhydantoin sodium and small doses of phenobarbital in combination with atropine. On this therapy he showed a striking improvement. His blackouts subsided completely, and he was able to resume his work. There remained, however, mild paresthesias in the chest and arms. On reexamination Chvostek's sign could be elicited and the serum calcium level was found to be 7.5 mg. per hundred cubic centimeters. He then was given calcium gluconate parenterally, which resulted in prompt disappearance of the paresthesias. He has been well for the past fifteen months. However another electroencephalogram taken after three months of treatment when the patient was free from symptoms showed a pattern similar to that obtained before the treatment was begun.

CASE 2.—The patient, a white woman 40 years of age, had symptoms even as a young girl. For a number of years she occasionally felt "something of a barrier between herself and other people" and sometimes felt "as if she were doped." During the depression of 1929 her father committed suicide and the patient, 15 years old at that time, began to suffer from claustrophobia. Two months before she was first seen by us (in 1944) she had acute pyelitis, and shortly thereafter she lost her appetite. As a result her weight declined appreciably. A number of symptoms then developed, such as chills and profuse sweats, coldness in the extremities, excessive hunger, crying spells associated with shaking and tingling sensation and double vision. After two weeks' observation in a hospital she was discharged, with the diagnosis of pulmonary tuberculosis and psychoneurosis. However the patient herself soon noticed that crying spells would disappear shortly after the intake of food but that if not enough food was eaten double vision would come back.

The physical examination was essentially noncontributory.

*Laboratory Findings.*—Roentgenograms of the chest showed old healed bilateral apical tuberculosis. A glucose tolerance test revealed spontaneous hypoglycemia

TABLE 1.—*Blood Glucose Levels (Milligrams per Hundred Cubic Centimeters) After Administration of One Hundred Grams*

	Case 1	Case 2*	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Before administration.....	77	94 97	81	94	86	97	86	75
½ hr. after administration...	104	94	74	121	126	131	107	101
1 hr. after administration...	93	94 136	66	115	115	82†	72†	123
1½ hr. after administration...	86	93	50†	..	74†	86	86	120
2 hr. after administration...	70	100 96	61	91	78†	68	76†	100
2½ hr. after administration...	69	83	68	..	86	79†	82	68†
3 hr. after administration...	62	84† 90†	55†	64†	62	77	73	52†

\* In this case the tolerance test was carried out twice.

† Hypoglycemic symptoms such as weakness, dizziness, excessive perspiration, nervousness, crying spells, fainting spells and epigastric distress were demonstrated.

(table 1). The serum calcium level was 9.7 mg. per hundred cubic centimeters, and the basal metabolic rate was —8 per cent. The electroencephalogram showed abnormal electrocortical activity over the entire cortex evidenced by random and short series of waves of 6 to 8 cycles per second. Hyperventilation resulted in several bursts of high voltage activity of 3 to 4 cycles per second. The pattern was the type frequently noted in convulsive disorders.

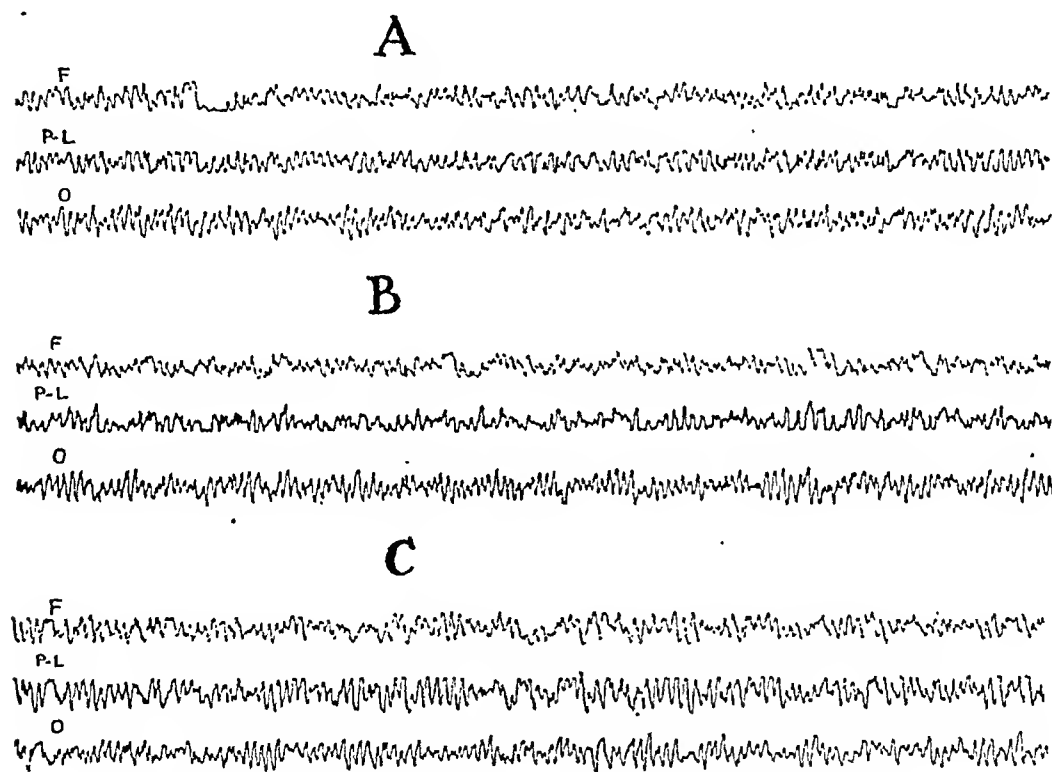
The treatment consisted of a diet for hypoglycemia and the administration of diphenylhydantoin sodium, phenobarbital and small doses of atropine. Occasionally dextroamphetamine sulfate was also prescribed. The patient responded to this treatment satisfactorily and had mild symptoms only after overwork or when she did not eat enough. A recurrence of moderate symptoms was observed during a three week period of virus pneumonia, but the patient has remained free from symptoms for the last two years.

CASE 3.—A married woman aged 29 years gave a history of having suffered for years from nervousness, crying spells, insomnia, fatigue, depression, anxiety and "fear of impending disaster." Crying spells and spells of depression would

end abruptly for no apparent reason and occasionally were followed by a feeling of well-being and optimism. She also had headaches on arising in the morning, which often lasted throughout the day.

In this case the correct diagnosis was first missed. Because of helminthiasis and low grade anemia the patient was first given hexylresorcinol and methylrosaniline chloride and then ferrous sulfate and parenteral injections of liver extract with vitamin B complex. She felt somewhat improved, but soon the old complaints came back. It was then thought that they might be related to financial troubles and marital problems, and the patient was referred to a psychiatrist. However, she did not respond to psychotherapy, and her depression became intensified. Three years after she was first seen she was reexamined by one of us (M. F.). This time a more detailed history was obtained.

Since childhood the patient had been subject to spells of weakness associated with confusion and frequent episodes of drowsiness, and she often lived in a dazed



Electroencephalographic tracings. *A*, case 1; *B*, case 4; *C*, case 6.

state of mind. She was unable to concentrate and unable to make a success of anything. There was also a history of moaning and muscular twitchings during the night. In recent years a change of personality occurred. She quarreled for trivial reasons and threw objects in frenzies of anger. Afterward there was always abysmal shame and regret for this behavior, but she was unable to control it.

Because of this history the possibility of an epileptic state was considered. The electroencephalogram was abnormal as indicated by random waves of 6 to 8 cycles per second and occasional increased voltage discharges of 7 cycles per second rhythm. Hyperventilation increased the 6 to 7 cycles per second activity. The tracing was considered consistent with a convulsive tendency or with a generalized physiologic cerebral disturbance.

With anticonvulsive therapy there was some improvement, but the results were unsatisfactory and the patient continued to have mild spells. Then a glucose toler-



ance test was made and gave results typical of spontaneous hypoglycemia (table 1). The serum calcium level was found to be 8.7 mg. per hundred cubic centimeters. When the anticonvulsive therapy was supplemented by proper diet for hypoglycemia the patient gained 14 pounds (6.4 Kg.) in three weeks and showed a rapid and striking improvement. The daily crying spells ceased. She was able not only to work without undue fatigue but also to complete a year's course of chemistry with the idea of becoming a laboratory assistant.

CASE 4.—A married woman aged 24 years had had attacks of sudden weakness and fainting spells for about a month. The first attack occurred after nine hours of driving to attend her grandfather's funeral. At the breakfast table she had "a feeling of numbness and of going away," and she then began to dry dishes automatically. After ten minutes she felt exhausted, frightened and extremely sleepy, but she was afraid to go to sleep. The physician who examined her at that time found a blood pressure of 160 systolic and 100 diastolic, which an hour later was 138 systolic and 80 diastolic. The second attack occurred three weeks later around 10:30 in the morning. She was reading to her sick son when suddenly she felt panicky and short of breath. A physician who examined her half an hour later ascribed the symptoms to nervousness. The third attack occurred a week later, again around 10 a.m. She was working and "felt wonderful when suddenly she began to feel shaky inside, scared and very lonely."

Even as a child the patient was extremely nervous and had tremor of the hands, especially when excited. During the two years preceding her first visit to us she exhibited muscular twitchings while asleep during the night. Her diet in the past few years had been inadequate and the distribution of meals incorrect. She had breakfast early in the morning and then ate little or nothing until supper time.

The physical examination revealed nothing abnormal except for tremor of the hands and a slightly positive Romberg sign.

*Laboratory Data.*—The reaction to the glucose tolerance test was typical of spontaneous hypoglycemia (table 1), the serum calcium level was 7.6 mg. per hundred cubic centimeters and the basal metabolic rate was slightly increased on two occasions, i.e., + 17 and + 22 per cent. The electroencephalogram was abnormal and showed frequent trains of high amplitude 7 to 8 cycles per second rhythm in addition to random 6 cycles per second potentials. Hyperventilation increased the incidence of the slow activity. The tracing was considered to be highly consistent with a convulsive tendency (figure).

She made a prompt response to the dietary management supplemented with diphenylhydantoin sodium and phenobarbital. She was also given calcium gluconate parenterally. A few mild attacks occurred after emotional upsets or omission of meals, but on the whole she was greatly improved and was able to go through another pregnancy without untoward symptoms.

CASE 5.—A young woman 22 years of age enjoyed good health until four years before her first visit to one of us (M. F.). At that time attacks of weakness, nervousness and trembling developed. The attacks usually came on around 4 o'clock in the afternoon and were relieved by the intake of sweet beverages. She also complained of headaches, depression and crying spells. Her physician made a diagnosis of hyperthyroidism and prescribed rest and a diet. On this regimen she improved, but the symptoms repeated themselves on two occasions after a decline in weight. In recent months she had lost some 10 pounds (4.5 Kg.), and her attacks had recurred once more.

The physical examination revealed only tremor of the hands and a slightly positive Chvostek sign.

*Laboratory Data.*—The reaction to the glucose tolerance test was characteristic of spontaneous hypoglycemia. The serum calcium level was 8.2 mg. per hundred cubic centimeters, the blood count revealed the presence of slight anemia (hemoglobin content 82 per cent and red blood cells 3,740,000) and the basal metabolic rate was —5 per cent. The electroencephalogram was abnormal as evidenced by a predominant fast type of record with occasional 7 to 8 cycles per second potentials. Hyperventilation increased the voltage output of the fast activity.

The patient was given liver extract in combination with vitamin B complex, phenobarbital and diphenylhydantoin sodium, and in addition she was given a diet for hypoglycemia. She responded well to this therapy, but her symptoms were not controlled completely until injections of calcium gluconate were substituted for the liver extract and the vitamin B complex.

CASE 6.—A 21 year old woman, sister of the patient in case 4, had been having attacks for four months. The attacks consisted of abdominal pain, nausea, vomiting, numbness in the head, shaking, sensation of being limp, weakness, exhaustion, depression and crying spells. She was afraid of people and afraid of being alone. In the three months preceding the onset of symptoms her weight dropped from 112 (50.8 Kg.) to 99 pounds (45 Kg.).

Physical examination showed only tremor of the hands and markedly exaggerated reflexes.

*Laboratory Data.*—The result of the test of glucose tolerance is given in table 1. The basal metabolic rate on the first examination was +53 per cent; a month later it was +26 per cent, and after four months of treatment it dropped to —8 per cent. The serum calcium level was 7.9 mg. per hundred cubic centimeters. The blood count showed a hemoglobin content of 82 per cent and 3,900,000 red blood cells. The electroencephalogram was abnormal, as evidenced by much 5 to 8 cycles per second activity in the tracing (figure). The record was interpreted as consistent with some diffuse cerebral disturbance or with a convulsive tendency.

The treatment in this case consisted of dietary management of hypoglycemia and the administration of diphenylhydantoin sodium, phenobarbital and occasionally dextroamphetamine sulfate. The patient also received calcium gluconate and liver extract with vitamin B complex parenterally for a period of four weeks. The response to this therapy was excellent, and she was able to resume her study of music. After a few weeks of treatment she was able to work at her piano up to eight hours a day. In the past eighteen months she has experienced recurrences of mild symptoms only during menstrual periods, after emotional upsets or when her meals have been delayed.

CASE 7.—A 33 year old housewife, sister of the patient in case 3, had had crying spells even as a child but otherwise had been in good health until the age of 17. She then felt unusually tired and slightly dizzy. Her fatigue became particularly worse at the age of 25 after she got married. On account of her husband's irregular working hours she could not eat properly or sleep enough, and her weight declined from 115 (52 Kg.) to 99 pounds (45 Kg.). The vertigo, which was rather slight in previous years, became so accentuated that occasionally she would lose her balance on turning around quickly or on awakening, in which case the vertigo disappeared after breakfast. She also complained of inability to concentrate and of feeling excessively hungry and irritable before lunch and dinner.

The physical examination was essentially noncontributory except that slight tenderness was revealed in the right upper abdominal quadrant. The laboratory

findings of interest were a hemoglobin content of 92 per cent, a red blood cell count of 3,880,000 and the presence of ova of *Ascaris* in the feces.

After the administration of santonin she expelled six worms, and she then was given ferrous sulfate by mouth and liver extract with vitamin B complex parenterally. She was not seen again until three years after her first visit. This time she reported that some two years previously she had had her second child. Her general condition seemed to have deteriorated recently, and she lost some weight. She wondered if she could not be benefited by the therapy which had done so much good for her sister.

The laboratory examination this time revealed the presence of spontaneous hypoglycemia (table 1) and a serum calcium level of 7.3 mg. per hundred cubic centimeters. The blood count showed a hemoglobin content of 83 per cent and a red blood cell count of 3,800,000. The electroencephalogram was slightly abnormal as indicated by an occasional 6 to 8 cycles per second potential. Hyperventilation produced a few short bursts of 6 cycles per second rhythm.

The therapy in this case consisted of a diet for hypoglycemia and the parenteral administration of liver extract alternately with calcium gluconate. The patient was also given diphenylhydantoin sodium, ferrous sulfate and vitamin B complex. Within a few weeks her condition was greatly improved and she lost completely the feeling of undue fatigue. In four months she gained over 14 pounds (6.4 Kg.). A blood count taken about two months after the treatment was begun was found to be normal, whereupon administration of liver extract and iron was stopped. She continues to take diphenylhydantoin sodium, and occasionally she takes dextroamphetamine sulfate once or twice daily. The only remnant of her original symptom complex in the past year were spells of depression, and they were infrequent and of short duration.

CASE 8.—A white man aged 36 years suffered from digestive disturbances for over fifteen years. He also complained of nervousness, restlessness, dizziness and spells of depression and anxiety. He was being treated for duodenal ulcer, and the physicians under whose care he had been ascribed his nervous condition to the persistence of the duodenal condition.

On physical examination deep tenderness was found in the right upper and right lower abdominal quadrants. Roentgenologic studies revealed a gallbladder filled with stones and chronic appendicitis. Surgical intervention was advised, and cholecystectomy and appendectomy were carried out. At the operation the clinical diagnosis of cholelithiasis and chronic appendicitis was confirmed and the search for a possible gastric or duodenal ulcer was fruitless. After the operation the patient's digestive symptoms subsided, but within six months he began to experience gassy distention and abdominal discomfort. He was extremely nervous and irritable. He felt fatigued and was without ambition. At this point he consulted one of us (M. F.) again. He complained about a fear of impending danger. He feared that the operation was not successful, that cancer had been found in his stomach and that there was no hope for him. Although a man of relative wealth, he was greatly concerned about the financial security of his wife and daughter.

On examination he appeared unhappy, tense and restless and exhibited a slight tremor of both hands.

The laboratory findings were as follows: The blood count as well as the blood cholesterol and ester levels were normal. The serum calcium was 9.6 mg. per hundred cubic centimeters. The basal metabolic rate was +16 per cent. There was marked gastric hyperacidity, and the stools contained a large number of poorly digested muscle fibers. After oral administration of dextrose a notable

drop in the glucose content of the blood occurred in the third hour (table 1), and this decline was accompanied with weakness, dizziness and perspiration. These symptoms subsided promptly after he had taken a glass of orange juice.

The electroencephalogram was abnormal as evidenced by a fast type of record which showed numerous sharp formations and an occasional wave of 6 to 8 cycles per second. Hyperventilation resulted in random 5 cycles per second potentials and increased the 6 to 8 cycles per second activity.

The patient was given a diet for hypoglycemia and gastric hyperacidity and also diphenylhydantoin sodium and small doses of phenobarbital in addition to medication for the digestive disorders. Since he was observed for only three months before this paper was completed, it is too early to report on the final effect of the prescribed therapy. It may, however, be mentioned that his digestive symptoms have subsided, his nervous condition has improved remarkably and his personality traits have become more or less normal.

'TABLE 2.—*Symptoms Common to Spontaneous Hypoglycemia and Cerebral Dysrhythmia*

Symptoms	No. of Cases	Symptoms	No. of Cases
Dizziness.....	7	Mental dulness.....	4
Tendency to faints.....	8	Fear.....	7
Temporary blackouts.....	6	Bursts of temper.....	6
Sudden weakness.....	7	Automatic action.....	4
Paresthesias.....	7	Crying spells.....	6
Shaky feeling.....	6	Behavioristic changes.....	8
Tremor.....	6	Palpitation.....	7
Muscular twitchings.....	5	Difficult breathing.....	5
Convulsions.....	2	Pallor.....	6
Restlessness.....	6	Hot flushes.....	3
Headaches.....	7	Perspiration.....	5
Migraine.....	3	Shivering.....	6
Depression.....	8	Nausea.....	7
Confusion.....	7	Vomiting.....	2

*Symptoms Common to the Three Conditions.*—A number of symptoms observed in our patients are of a nature common to both spontaneous hypoglycemia and cerebral dysrhythmia. Table 2, in which the most frequent of these symptoms are listed, shows clearly that any of these conditions could account for the clinical picture presented by the patients. The same applies to the symptoms which are commonly observed in spontaneous hypoglycemia and parathyroid insufficiency, which are represented in table 3.

The distribution of the most outstanding symptoms was as follows: A tendency to faint, depression and personality changes were observed in all patients. Headaches, dizziness, foggiess and anxiety were frequently encountered. Sudden fatigue and muscular weakness, tenseness and restlessness and palpitation were present in all patients with hypocalcemia. Crying spells were noted in all female patients.

*Time at Which Symptoms Occurred.*—Symptoms occurred mainly within one-half to two hours or occasionally up to four hours after meals. The patient in case 3 experienced malaise, extreme nervousness and confusion frequently within fifteen minutes after eating. She and the patient in case 4 were the only ones in the entire group who exhibited symptoms during the night (groaning, restlessness and muscular twitchings). The patient in case 1 was subject to frequent fainting spells on arising in the morning.

It is generally accepted that manifestations of spontaneous nonorganic hypoglycemia appear within two to four hours after meals. There are, however, some reports in the literature which do not seem compatible with this view. Labbé,<sup>1</sup> for instance, observed a case in which severe symptoms with loss of consciousness occurred within a few minutes

TABLE 3.—*Symptoms Common to Spontaneous Hypoglycemia and Hypocalcemia*

Symptoms	No. of Cases	Symptoms	No. of Cases
Dizziness.....	5	Crying spells.....	5
Shortness of breath.....	4	Bursts of temper.....	4
Fatigue and muscular weakness....	6	Anxiety or fear of impending disaster.....	5
Tendency to faints.....	6	Depression.....	6
Temporary blackouts.....	5	Behavioristic changes.....	6
Paresthesias.....	5	Pallor.....	4
Shaky feeling.....	5	Hot flushes.....	2
Tremor.....	5	Perspiration.....	4
Muscular twitchings.....	4	Shivering.....	5
Convulsions.....	2	Palpitation.....	6
Headaches.....	5	Nausea.....	5
Migraine.....	2	Vomiting.....	1
Tenseness and restlessness.....	6		

after the ingestion of food. In another case observed by the same author<sup>2</sup> malaise, weakness, vertigo, diplopia, excessive hunger and epigastric pain came on within a few minutes after meals. Our own experience seems to indicate that the clinical state of nonorganic hypoglycemia may develop within fifteen minutes after a meal as well as in the post-absorptive state.

*Correlation Between Clinical Symptoms and the Blood Sugar Values.*—The fasting blood sugar levels in our group of patients were within the normal range (75 to 97 mg. per hundred cubic centimeters). The curves for glucose tolerance were rather flat, and the peak of the rise did not exceed 131 mg. Levels lower than the initial ones were obtained for all patients within one-half to two and a half hours after administra-

1. Labbé, M.; Brulé, M., and Lenègre: Un cas d'hypoglycémie spontanée avec amélioration persistante, Bull. et mém. Soc. méd. d. hôp. de Paris 48:101, 1932.

2. Labbé, M.; Boulin, R., and Petresco, M.: Hypoglycémie alimentaire, Bull. et mém. Soc. méd. d. hôp. de Paris 48:181, 1932.

tion of dextrose. An attempt at spontaneous recovery from low blood sugar levels was seen in 5 cases (cases 2, 3, 5, 6 and 7), but actual return to fasting values during the three hour period of observation was noted only in cases 5 and 7. The clinical symptoms of hypoglycemia coincided with the decrease of the blood sugar to below the initial level even when the glucose concentration did not descend to definitely hypoglycemic values, so that the symptoms were often out of proportion to the actual blood sugar values.

The current opinion is that the demonstration of a sufficiently low blood sugar level during attacks is a prerequisite to the diagnosis of hypoglycemia. In our cases we have not found such a correlation between the concentration of glucose in the blood and the clinical symptoms. The attacks occurred when there were normal or mildly decreased levels. That they were related to variations in the blood glucose concentration, however, is borne out by the fact that they were promptly relieved by administration of sugar and that they subsided when the rebound rise in the blood sugar level took place even when this rise was not significant. Discrepancies between the laboratory evidence and the clinical state of hypoglycemia in various clinical and experimental conditions have been reported by a number of investigators. In a group of diabetic persons studied by John<sup>3</sup> insulin reactions coincided with low blood sugar levels in only 54 per cent. Similarly, Sevringhaus and others<sup>4</sup> have observed that reactions produced by administration of insulin in normal subjects may appear when the blood sugar is at various levels. Hypoglycemic symptoms may be absent when there are low blood sugar levels in diabetic persons treated with insulin,<sup>5</sup> as well as in hyperinsulinism of pancreatic origin.<sup>6</sup> Conversely, severe attacks may occur in hyperinsulinism when the levels are comparatively high,<sup>7</sup> while in hypoglycemia caused by adrenal insufficiency<sup>8</sup> or by starvation<sup>8a</sup> clinical

3. John, H. J.: The Lack of Uniformity in the Insulin Reaction, *Am. J. M. Sc.* **172**:96, 1926.

4. Sevringhaus, E. L.; Kirk, E., and Heath, H. J.: The Duration and Magnitude of the Hypoglycemia After Insulin, *Am. J. M. Sc.* **166**:677, 1923.

5. Peters, C. A., and Rabinowitch, I. M.: A Case of Diabetes Mellitus Showing Aglycemia Without Symptoms, *Am. J. M. Sc.* **178**:29, 1929.

6. (a) Romano, J., and Coon, G. P.: Physiologic and Psychologic Studies in Spontaneous Hypoglycemia, *Psychosom. Med.* **4**:283, 1942. (b) Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*, Philadelphia, W. B. Saunders Company, 1941.

7. Mosenthal, H. O.; Ashe, B. I.; Poindexter, C. A., and MacBrayer, R.: Spontaneous Hypoglycemia Occurring in the Course of Essential Hypertension, *M. Clin. North America* **17**:41, 1933.

8. (a) Engel, G. L., and Margolin, S. G.: Neuropsychiatric Disturbances in Internal Disease: Metabolic Factors and Electroencephalographic Correlations, *Arch. Int. Med.* **70**:236 (Aug.) 1942. (b) Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, *J. Clin. Investigation* **19**:813, 1940.

manifestations may develop when the blood glucose concentration is higher than that in normal subjects during attacks.

In explanation of the lack of parallelism between clinical symptoms of hypoglycemia occurring after administration of insulin and the blood sugar values in diabetes, it has been postulated that the rapidity with which the blood sugar level falls is the factor responsible for the reactions. An alternative explanation of a similar lack of parallelism in spontaneous hypoglycemia may be that rapid variations in the blood sugar concentration are missed even when the determinations are made around the time of the attacks. Likewise, when blood samples are taken routinely every one-half to one hour during glucose tolerance tests the lowest blood sugar values may not be recorded. Labbé and his associates<sup>2</sup> obtained the following response to administration of dextrose in the aforementioned case of spontaneous hypoglycemia with severe reactions within a few minutes after the intake of food:

	Glucose Content, Mg./100 Cc.
Before administration .....	115 112
Fifteen minutes after administration...	46 38
Thirty minutes after administration....	135 122

These explanations do not seem, however, to apply to our patients since we have found no precipitous drop of the blood sugar level in the course of tolerance tests or critically low levels during most of the attacks. To overcome the inconsistency of hypoglycemic manifestations in the absence of markedly decreased blood sugar values, Himwich<sup>9</sup> has suggested that sugar level in the brain might be lower than that in the blood in some patients with hypoglycemia. As mentioned earlier, venous blood was used in the determination of glucose levels in our study, and it may be assumed that the glucose concentration in the arterial cerebral circulation was rather higher than that obtained in the venous blood. However, in extension of Himwich's hypothesis, it is conceivable that with variations of the blood sugar within the normoglycemic or slightly hyperglycemic range and with a normal availability of glucose in the brain there may be some disturbance in the uptake or utilization of glucose by this organ depriving it of adequate energy. This concept is not out of line with general biochemical experience, but the experimental support is lacking to answer the question one way or another. At present, the lack of correlation between clinical and laboratory findings in hypoglycemia may be taken to mean that the lowering of the glucose level in the circulating blood is not the only factor involved in the production of the clinical state of hypoglycemia. Accordingly, with regard to our patients we are inclined to assume that there was a certain degree of hypersensitivity or some peculiar reactivity to relatively

9. Himwich, H. E.: Personal communication.

minor fluctuations of the blood sugar level. This hypersensitivity may possibly be related to the occurrence of changes in the brain waves or to the instability of the autonomic nervous system which was noted in all of them.

Since the parallelism between blood sugar values and hypoglycemic symptoms is not so strict as it is claimed to be, we feel that the inability to demonstrate subnormal blood sugar levels during attacks should not be used to preclude the diagnosis of spontaneous extrapancreatic hypoglycemia. In our opinion the finding of an abnormally low curve for glucose tolerance in cases in which the clinical picture of this condition is presented is an important and sufficient diagnostic criterion.

*Effect of Exercise.*—It is a known fact that physical activity is followed by a lowering of the blood sugar level and can precipitate hypoglycemic symptoms, especially in subjects with instability of the vegetative nervous system (the so-called effort hypoglycemia of Bickel). Of all our patients, only 1 (case 3) demonstrated this phenomenon. This patient had definite symptoms after one to one and a half hours of housework. The other patients failed to notice any effect of physical effort on their condition. Of interest in this respect are observations made by Labbé<sup>1</sup> in a case of spontaneous hypoglycemia already mentioned. The patient experienced no discomfort after a walk of 10 kilometers in seventy minutes. His blood sugar level before the walk was 74 mg. per hundred cubic centimeters and after the walk 76 mg. Similarly, in a case of hyperinsulinism reported by Mosenthal<sup>7</sup> the blood sugar was 79 mg. per hundred cubic centimeters after the patient had walked thirty blocks. It would therefore appear that physical activity has no constant effect on the sugar concentration in the blood and on the symptomatology of hypoglycemia.

*Correlation Between Electroencephalographic Changes and Clinical Symptoms.*—Figure 1 illustrates three representative electroencephalograms which show that the patterns in our patients consisted for the most part of a slow type of alpha (8 to 9.5 cycles per second) rhythm and random 6 to 7 cycles per second potentials. These are classified as mildly abnormal or borderline tracings. Records of this type are frequently found for epileptic patients who have only infrequent or rare seizures. They are also observed in approximately 10 per cent of clinically normal controls but are believed by some to be indicative of a "convulsive tendency." It is questionable, however, whether one could diagnose clinical disorders such as spontaneous hypoglycemia and cerebral dysrhythmia purely on the basis of electroencephalographic observations, and we would hesitate to suggest that the patients in the group herewith presented necessarily have a convulsive tendency. It is possible, nevertheless, that patients with certain physiologic disturbances or



metabolic changes which are accompanied with alterations of the electroencephalographic pattern of the type described in this paper may have a decreased threshold for the development of convulsions or epileptiform reactions when compared with persons who have entirely normal electroencephalograms. As a result of a lowered threshold for the development of epileptic-like reactions such persons may be predisposed to exhibit symptoms under physiologic stress or disturbance.

#### TREATMENT

We have used the following therapeutic measures:

1. Dietary management of hypoglycemia. We have found that a maintenance diet high in protein as recommended by Conn<sup>10</sup> is superior to any other dietary system used in this condition. However, we have obtained better results when small feedings were interposed between the three main meals and a meal was added before bedtime.

2. Medication. This was individualized according to the patients' symptoms and their response to treatment. All our patients at one time or another took small doses of phenobarbital in combination with belladonna or atropine. We are of the opinion that this combination is more effective than phenobarbital alone. The use of atropine is justified for two reasons: first, because it might favorably influence spontaneous hypoglycemia;<sup>11</sup> second, because it can prevent or inhibit the effect of acetylcholine on the electrical activity of the cortex.

In our experience phenobarbital alone was not adequate in the control of symptoms which could be ascribed to abnormal cerebral discharges. The response was rapid and striking when diphenylhydantoin sodium was substituted for phenobarbital or taken in conjunction with it even when there was no history of convulsions or psychomotor manifestations. Dextroamphetamine sulfate proved a valuable adjunct in patients with decided depression. Calcium salts were used, with excellent results, both parenterally and orally in cases which were associated with hypocalcemia. Finally, we have also given vitamin B complex with nicotinic acid for depression of mood, confusion and a dazed state of mind. This therapy, however, seemed to have only a temporary effect.

3. Psychotherapy. Evidence of emotional and autonomic instability was noted in all our patients. In addition the uncertain medical outlook

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10. Conn, J. W.: The Advantage of a High Protein Diet in the Treatment of Spontaneous Hypoglycemia: Preliminary Report, *J. Clin. Investigation* **15**: 673, 1936.

11. Harris, S.: Hyperinsulinism, a Definite Disease Entity: Etiology, Pathology, Symptoms, Diagnosis, Prognosis and Treatment of Spontaneous Insulogenic Hypoglycemia (Hyper-Insulinism), *J. A. M. A.* **101**:1958 (Dec. 16) 1933.

which they had before the symptoms were relieved doubtlessly played a significant part in the persistence or exacerbation of their symptoms. As mentioned before, psychotherapy of itself was of no appreciable value in this group of patients, but we are convinced that it can play a useful role. Such patients feel highly apprehensive and destined for failure. They can be made to understand that they are not neurotic and that they are suffering from functional disorders which can be corrected, and they should be encouraged to resume their normal place in family and society.

#### COMMENT

Hypoglycemia was reported in the literature as a factor in the production of epileptic seizures.<sup>12</sup> However, since the clinical picture of hypoglycemia itself may be indistinguishable from epilepsy, the earlier reports in which the diagnosis of epilepsy was not supported by electroencephalographic evidence are open to criticism. Recent investigators<sup>13</sup> failed to detect any relationship between the variations of the blood sugar concentration and the clinical manifestations of epilepsy and have noted that distinctly hypoglycemic blood sugar values occurring after the administration of dextrose do not produce epileptic seizures. Similarly, it was shown that hypoglycemia following administration of insulin does not precipitate epileptic convulsions or attacks of petit mal.<sup>14</sup>

Gibbs and others<sup>15</sup> have studied the effect of variations in the glucose level of the blood on the electroencephalographic pattern. They have found that in normal subjects a blood sugar concentration of 50 mg. per hundred cubic centimeters does not produce abnormal brain potentials while a concentration of 30 mg. or less may be associated with changes which differ from those recorded in epilepsy. In epilepsy of the grand mal and psychomotor type large doses of insulin had no effect on the abnormal electrical activity of the brain while in the petit mal type

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12. Harris, S.: Epilepsy and Narcolepsy Associated with Hyperinsulinism: Report of Three Cases of Epilepsy and of One Case of Narcolepsy Cured Clinically by Partial Resection of Body and Tail of Pancreas, *J. A. M. A.* **100**:321 (Feb. 4) 1933. Labbé, M.; Armand-Delille, P. F., and Goldberg: Diabète et épilepsie, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:1552, 1932.

13. (a) Lennox, W. G.: Studies of Metabolism in Epilepsy: II. The Sugar Content of the Blood, *Arch. Neurol. & Psychiat.* **18**:383 (Sept.) 1927; (b) Studies in Metabolism in Epilepsy: III. The Blood Sugar Curve, *ibid.* **18**:395 (Sept.) 1927. (c) Lennox, W. G., and Cobb, S.: Epilepsy from the Standpoint of Physiology and Treatment, *Medicine* **7**:105, 1928. (d) Pollock, L. J., and Boshes, B.: Carbohydrate Metabolism in Epilepsy, *Arch. Int. Med.* **59**:1000 (June) 1937.

14. Baudouin, A.; Azérad, E., and Lewin, J.: Epreuve d'hypoglycémie insulinique chez les épileptiques, *Compt. rend. Soc. de biol.* **114**:902, 1933. Lennox.<sup>13b</sup> Pollock.<sup>13d</sup>

15. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Influence of the Blood Sugar Level on the Wave and Spike Formation in Petit Mal Epilepsy, *Arch. Neurol. & Psychiat.* **41**:1111 (June) 1939.

a drop in the blood sugar value to 50 mg. or less per hundred cubic centimeters enormously accentuated the abnormal brain pattern. Similarly, Davis<sup>16</sup> found no correlation between the fasting blood sugar level and the electroencephalographic pattern of normal subjects. Low blood sugar values after intravenous administration of insulin had no effect on the initially normal electroencephalograms but enhanced dysrhythmic activity when there were abnormal patterns before insulin was given.<sup>17</sup> Williams<sup>18</sup> noted an increase in cerebral discharges in cases of petit mal after administration of chloryl and acetylcholine, but he failed to find any relationship between the amount of abnormal cortical activity and the rather small fluctuations of the blood sugar values.

Alterations of cortical activity in the course of insulin shock therapy parallel the decrease in the blood sugar level,<sup>19</sup> and after administration of dextrose or during spontaneous awakening the electroencephalogram becomes normal even when the blood sugar values remain low. Correlation between low glucose concentrations in the blood and electroencephalographic abnormalities has been found in animals given injections of insulin<sup>20</sup> or after hepatectomy.<sup>21</sup> Similar observations have been made also in some cases of hyperinsulinism of pancreatic origin in man,<sup>22</sup> while in others no electroencephalographic abnormalities

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16. Davis, P. A.: Technique and Evaluation of the Electroencephalogram, *J. Neurophysiol.* **4**:92, 1941.

17. Davis, P. A.: Effect on the Electroencephalogram of Changing Blood Sugar Level, *Arch. Neurol. & Psychiat.* **49**:186 (Feb.) 1943.

18. Williams, D.: The Effect of Cholin-Like Substances on the Cerebral Electrical Discharges in Epilepsy, *J. Neurol. & Psychiat.* **4**:32, 1941.

19. Himwich, H. E.; Frostig, J. P.; Fazekas, J. F., and Hadidian, Z.: The Mechanism of the Symptoms of Insulin Hypoglycemia, *Am. J. Psychiat.* **96**:371, 1939. Himwich, H. E.; Hadidian, Z.; Fazekas, J. F., and Hoagland, H.: Cerebral Metabolism and Electrical Activity During Insulin Hypoglycemia in Man, *Am. J. Physiol.* **125**:578, 1939. Hoagland, H.; Cameron, D. E., and Rubin, M. A.: The Electroencephalogram of Schizophrenics During Insulin Treatments, *Am. J. Psychiat.* **94**:183, 1937. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, *Am. J. Physiol.* **120**:559, 1937.

20. Gellhorn, E., and Kessler, M.: The Effect of Hypoglycemia on the Electroencephalogram at Varying Degrees of Oxygenation of the Blood, *Am. J. Physiol.* **136**:1, 1942.

21. Maddock, S.; Hawkins, J. E., Jr., and Holmes, E.: The Inadequacy of Substances of the "Glucose Cycle" for Maintenance of Normal Cortical Potentials During Hypoglycemia Produced by Hepatectomy with Abdominal Evisceration, *Am. J. Physiol.* **125**:551, 1939.

22. Hoefler, P. F. A.; Guttman, S. A., and Sands, I. J.: Convulsive States and Coma in Cases of Islet Cell Adenoma of the Pancreas, *Am. J. Psychiat.* **102**:486, 1946. Strauss, H., and Wechsler, J. S.: Clinical and Electroencephalographic Studies of Changes of Cerebral Function Associated with Variations in the Blood Sugar, *ibid.* **102**:34, 1945.

were noted.<sup>8a</sup> In hypoglycemia produced by adrenal insufficiency or starvation the electroencephalographic abnormalities are less conspicuous, and they subside with the clinical improvement of the patients.<sup>8a</sup>

From this review of the literature it becomes evident that there is no correlation between hypoglycemic blood sugar values and epileptic convulsions. On the other hand, a low concentration of sugar in the blood may aggravate the electroencephalographic changes in patients with petit mal, while in normal subjects it may cause nonspecific alterations of the electroencephalogram but does not produce an epileptic type of brain activity. Furthermore, the abnormal patterns in severe hypoglycemia of both the spontaneous type and that induced with exogenous insulin are observed only during the state of hypoglycemia and are well correlated with excessively low blood sugar values. Also, they are of a transient nature and disappear with even insignificant rises in the concentration of glucose in the blood.

In contrast, our patients exhibited abnormal electrocortical activity without a profound lowering of the blood sugar level, and this abnormality persisted even when the patients were clinically cured. Furthermore, the treatment of only one of the coexisting conditions (electrocerebral dysfunction or hypoglycemia) failed to bring about complete and satisfactory results. Two patients (cases 1 and 2) in whom the treatment of hypoglycemia was continued without interruption experienced an aggravation of their condition when anticonvulsive therapy was discontinued. Two other patients (cases 3 and 6) took anticonvulsive drugs for months but continued to have mild symptoms. These subsided only when hypoglycemia was discovered and proper diet was prescribed and adhered to. From these considerations we feel justified in concluding that our patients had both spontaneous hypoglycemia and some cerebral disturbance which might or might not be related to a convulsive type of disorder.

The coexistence of spontaneous hypoglycemia with electrocerebral dysfunction raises the question as to the nature of their mutual relationship. Are they found together by simple coincidence or is there any etiologic link between them? Our knowledge at present is too scanty to answer this question satisfactorily. However, in the light of modern views on the electrochemical reactions involved in the formation and exchange of energy in body economy it appears conceivable that the two conditions may be somehow linked together.

Of especial interest are the recent investigations on the metabolism of acetylcholine and on its function in the central nervous system. It has been shown that this substance possesses high electrogenic prop-

erties<sup>23</sup> and is a powerful convulsant.<sup>24</sup> According to some,<sup>25</sup> disorders in the cerebral metabolism of acetylcholine may play an essential part in the causation or the mechanism of epileptic seizures in man.

Of particular significance are the following facts:

1. It has been demonstrated that the metabolism of acetylcholine is linked with carbohydrate metabolism. Quastel and his collaborators<sup>26</sup> have found glucose to be essential for the aerobic synthesis of acetylcholine by cortex slices. The optimal concentration of glucose for its stimulating action was below the normal blood range, while a concentration equal to normal blood sugar levels had an inhibitory effect. In keeping with these findings, Feldberg<sup>27</sup> has suggested that the normal blood sugar concentration has a restraining effect on the synthesis and release of acetylcholine in the central nervous system while at hypoglycemic levels these processes are markedly stimulated. In his opinion the effect of hypoglycemia on the metabolism of acetylcholine may explain the mechanism of hypoglycemic convulsions. Evidence that the anaerobic synthesis of acetylcholine is also linked with carbohydrate metabolism was obtained by Nachmansohn and Machado.<sup>28</sup>

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23. (a) Beutner, R., and Barnes, T. C.: Electrical Activity of Acetylcholine, *Science* **94**:211, 1941. (b) Feldberg, W., and Fessard, A.: The Cholinergic Nature of the Nerves to the Electric Organ of the Torpedo (*Torpedo Marmorata*), *J. Physiol.* **101**:200, 1942. (c) Gesell, R., and Hansen, E. T.: Anticholinesterase Activity of Acid as a Biological Instrument of Nervous Integration, *Am. J. Physiol.* **144**:126, 1945. (d) Miller, F. R.; Stavsky, G. W., and Woonton, G. A.: Effects of Eserine, Acetylcholine and Atropine on the Electrocorticogram, *J. Neurophysiol.* **3**:131, 1940.

24. (a) Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on the Electrical Activity of Cortex, *Arch. Neurol. & Psychiat.* **48**:382 (Sept.) 1942. (b) Miller.<sup>23d</sup>

25. Forster, F. M.: Action of Acetylcholine on Motor Cortex: Correlation of Effects of Acetylcholine and Epilepsy, *Arch. Neurol. & Psychiat.* **54**:391 (Nov.-Dec.) 1945. Brenner and Merritt.<sup>24a</sup>

26. (a) Mann, P. J. G.; Tennenbaum, M., and Quastel, J. H.: On the Mechanism of Acetylcholine Formation in Brain in Vitro, *Biochem. J.* **32**:243, 1938; (b) Acetylcholine Metabolism in the Central Nervous System: The Effects of Potassium and Other Cations on Acetylcholine Liberation, *ibid.* **33**:822, 1939. (c) Quastel, J. H.; Tennenbaum, M., and Wheatley, A. H. M.: Choline Ester Formation in, and Choline Esterase Activities of, Tissues in Vitro, *ibid.* **30**:1668, 1936.

27. Feldberg, W.: (a) Present Views on the Mode of Action of Acetylcholine in the Central Nervous System, *Physiol. Rev.* **25**:596, 1945; (b) Synthesis of Acetylcholine by Tissue of the Central Nervous System, *J. Physiol.* **103**:367, 1945.

28. Nachmansohn, D.; Cox, R. T.; Coates, C. W., and Machado, A. L.: Action Potential and Enzyme Activity in the Electric Organ of *Electrophorus Electricus*: Phosphocreatine as Energy Source of the Action Potential, *J. Neurophysiol.* **6**:383, 1943. Nachmansohn, D., and Machado, A. L.: The Formation of Acetylcholine; A New Enzyme: "Choline Acetylase," *ibid.* **6**:397, 1943.

2. The action of acetylcholine in nerve tissue is also related to calcium metabolism. Calcium was found to have an inhibitory effect on the formation of acetylcholine by brain tissue.<sup>29</sup> Moreover, it was shown that the degree of activity of a nerve cell produced by acetylcholine is dependent on the calcium content of the cell's environment. Higher concentrations of calcium diminish the rate of nerve activity and smaller concentrations increase it.<sup>30</sup>

With these data in mind it is tempting to assume that the syndrome of spontaneous hypoglycemia associated with electrocerebral dysfunction and hypocalcemia, which was described in this paper, may be caused by a common disturbance involving some profound alteration of the intracellular metabolism. It may also be assumed that as a result of this metabolic disorder all three factors involved in the syndrome (electrocerebral dysfunction, hypoglycemia and hypocalcemia) exceed a threshold tolerance and thus give rise to the clinical symptoms, while in the absence of the common metabolic disorder each factor separately may fail to produce the clinical symptomatology.

#### SUMMARY AND CONCLUSIONS

1. Eight cases of spontaneous hypoglycemia associated with electrocerebral dysfunction, in 6 of which the condition was also accompanied with hypocalcemia, are presented.

2. It is suggested that the coexistence of spontaneous nonorganic hypoglycemia with electrocerebral dysfunction and hypocalcemia be regarded as a clinical syndrome. It is assumed that the syndrome is produced by a common metabolic disorder which involves the metabolism of carbohydrates, acetylcholine and calcium. The recent literature in favor of this concept is reviewed.

3. Emphasis is laid on the similarity of symptoms in all three conditions on account of which their coexistence may be easily overlooked and the correct diagnosis missed.

4. The relation between the concentration of glucose in the blood and the clinical symptomatology of hypoglycemia is discussed. Cases studied were found not to conform to the accepted criteria for spontaneous nonorganic hypoglycemia. It is thought that these criteria are of questionable diagnostic value, and the literature in support of this view is presented.

5. It is postulated that the finding of an abnormally low curve for glucose tolerance in cases in which the clinical picture of spontaneous nonorganic hypoglycemia is presented is an adequate criterion for the diagnosis of this condition.

29. Feldberg.<sup>27a</sup> Mann, Tennenbaum and Quastel.<sup>26b</sup>

30. Bronk, D. W.: Synaptic Mechanisms in Sympathetic Ganglia, *J. Neurophysiol.* 2:380, 1939.

6. The electroencephalographic changes in this group of cases consisted for the most part of a slow type of alpha rhythm and random, 6 to 7 cycles per second potentials. These changes are not considered as indicative of epilepsy or of a convulsive disorder. They are assumed to reflect a decreased threshold for the development of epileptiform clinical reactions in persons suffering from metabolic disorders such as spontaneous hypoglycemia and hypocalcemia.

7. All patients responded satisfactorily to the therapy aimed at combating the associated conditions.

8. Observations presented in this paper make it clear that a careful search for the described syndrome should be made in selected cases in which a diagnosis of psychoneurosis is made. They also indicate that estimation of serum calcium levels should be made and electroencephalograms taken routinely in spontaneous hypoglycemia.

# DYNAMICS OF THE ACTION OF PENICILLIN

Time-Dose Relationship in Human Streptococcic Disease

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PENICILLIN now has almost reached the status of a panacea in medical therapy. Its value has been documented so completely that no further proof of its efficacy in the treatment of many bacterial infections is necessary, and the relative convenience of methods for its administration has been progressively more emphasized. Oral administration of penicillin has on the whole not fulfilled the expectations and has remained an expensive, wasteful and unreliable method. The vehicle proposed by Romansky<sup>1</sup> (peanut oil containing 4.8 per cent beeswax) has been found effective in maintaining penicillin blood levels for twenty-four hours after a single injection and has to some extent replaced aqueous solutions of penicillin in medical practice.

In spite of these advances the mechanism of the action of penicillin is still not entirely known. There is ample clinical evidence to show that sufficiently large doses must be given and that injections of simple aqueous solutions of penicillin must be administered at relatively frequent intervals. Eagle<sup>2</sup> has shown experimentally that in the treatment of rabbit syphilis at least the time-dose relationship is such that the total amount of penicillin necessary for cure is inversely proportional to the frequency and number of injections and that huge doses are necessary to provide cure with a single injection of penicillin. He also showed that in order to permit an arithmetical increase in the interval between doses of penicillin the size of the dose had to be increased geometrically. My experimental studies<sup>3</sup> of the treatment of fatal streptococcic infections in mice yielded essentially similar results. It was possible to effect cure with a single dose of sufficient

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From the United States Marine Hospital, San Francisco.

1. Romansky, M. J., and Rittman, G. C.: *Method of Prolonging Action of Penicillin*, Science **100**:196, 1944.

2. Eagle, H.; Magnuson, H. J., and Fleischman, R.: *The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis*, Bull. Johns Hopkins Hosp. **79**:168, 1946.

3. Jawetz, E.: *Dynamics of the Action of Penicillin in Experimental Animals: Observations on Mice*, Arch. Int. Med. **77**:1 (Jan.) 1946.



magnitude, and if several injections were given the size of the curative dose depended on the interval between injections. A logarithmical increase in the total dose of penicillin was essential to obtain an arithmetical increase of the survival rate of infected mice. Bloomfield<sup>4</sup> has demonstrated clinically that in some cases subacute bacterial endocarditis may be cured by the injection of aqueous penicillin twice daily.

The penicillin treatment of acute streptococcic disease is still somewhat controversial. Most workers agree that it produces striking subjective and objective clinical improvement and uniformly prevents septic complications.<sup>5</sup> If used for a sufficient length of time (variously claimed to be from four to seven days), it prevents the occurrence of relapses and greatly reduces the frequency of the carrier state. Recently it has been pointed out<sup>6</sup> in a report of a small series of patients that adequate penicillin therapy for acute streptococcic sore throat may prevent the late nonsuppurative complications such as carditis, fever, arthritis and the other manifestations of the post-streptococcic state.

The work presented here was undertaken in order to determine whether the results obtained in infections in experimental animals could be applied to human streptococcic diseases and to investigate some of the aspects of the time-dose relationship in short penicillin schedules which might result in more convenient methods of treatment.

#### EXPERIMENTAL STUDY

Eighty-one patients with streptococcic sore throat were treated under the various experimental penicillin schedules herein presented. They were merchant marines, and the majority were between the ages of 18 and 30 years. They were all ill and prostrated on their admission to the hospital, with temperatures of above 38.5 C. (101.3 F.), notable injection and edema of the throat, with some purulent exudate, and significantly enlarged tender cervical nodes. They had all been ill for less than seventy-two hours, and they were sufficiently uncomfortable

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4. Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis: Some Problems, *J. A. M. A.* **129**:1135 (Dec. 22) 1945.

5. Spink, W. W.; Rantz, L. A.; Boisvert, P. J., and Coggeshall, H.: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract: Evaluation in Tonsillitis, Nasopharyngitis and Scarlet Fever, *Arch. Int. Med.* **77**:260 (March) 1946. Plummer, N.; Duerschner, D. R.; Warren, H. D.; Rogliano, F. T., and Sloan, R. A.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, *J. A. M. A.* **127**:369 (Feb. 17) 1945. Hirsch, H. L.; Rotman-Kavka, G., and Sweet, L. K.: Penicillin Therapy of Scarlet Fever, *ibid.* **133**:657 (March 8) 1947.

6. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat: The Poststreptococcic State, *Arch. Int. Med.* **79**:401 (April) 1947.

to make hospitalization necessary. The diagnosis of streptococcic sore throat was established by the recovery of large numbers of beta hemolytic streptococci from the throat or nasopharynx and by the observance of the typical clinical picture. No serologic studies were performed. The patients were kept under close clinical observation for four to nine days after recovery. Throat cultures were taken at frequent intervals, and every attempt was made to determine bacteriologic relapses.

All patients were treated with commercial crystalline penicillin G according to the schedules presented in the tables. The immediate clinical response was evaluated by means of the return of the temperature and pulse to normal, by the subjective improvement and by the disappearance of all objective findings. Each schedule was evaluated as satisfactory or unsatisfactory according to the immediate clinical response observed and the frequency of clinical and bacteriologic relapses.

TABLE 1.—*Time-Dose Relationship in Penicillin Schedules for the Treatment of Streptococcic Sore Throat (Total Duration of Treatment Fixed)*

Schedule	No. of Days Treated	No. of Patients	Clinical Response	No. of Clinical Relapses	No. of Bacterio- logic Relapses	Result
5,000 units every 3 hr. $\times$ 32	4	4	Fair	3	3	Unsatisfactory
10,000 units every 3 hr. $\times$ 32	4	6	Good	1	2	Satisfactory
10,000 units every 6 hr. $\times$ 16	4	4	Fair	2	3	Unsatisfactory
20,000 units every 4 hr. $\times$ 24	4	14	Excellent	1	4	Satisfactory
40,000 units every 6 hr. $\times$ 16	4	8	Excellent	0	1	Satisfactory
80,000 units every 12 hr. $\times$ 8	4	4	Good	1	3	Unsatisfactory
150,000 units every 12 hr. $\times$ 8	4	12	Excellent	0	1	Satisfactory
300,000 units every 18 hr. $\times$ 5	4	3	Excellent	0	3	Unsatisfactory

Table 1 presents a summary of the results obtained with eight schedules in which the total duration of treatment was kept constant. It is clearly seen that within the scope of the experiment large doses at long intervals were just as effective as small doses given frequently. In order to compensate for an arithmetical increase in the interval between injections, a logarithmical increase in the size of the dose was necessary. This time-dose relationship applied only within certain limits. A minimal dose was necessary for satisfactory results even with frequent injections, and on the other hand doses could not be spaced apart more than twelve hours without much of the efficacy of the treatment being lost. With all "satisfactory" schedules the clinical response was immediate and the improvement strikingly rapid and streptococci disappeared from the throat within twenty-four hours. With the "unsatisfactory" schedules bacteriologic relapses occurred in from twenty-four hours to five days after treatment was discontinued and clinical symptoms recurred one to two days after the reappearance of organisms in the throat. A second series of patients were given a fixed dose at fixed intervals for a varying length of time (table 2). While

the immediate clinical response was uniformly satisfactory, it was not possible to shorten the treatment to less than four days without greatly increasing the chance of relapse. There were no suppurative complications in either group. The period of observation was too short for evidence of poststreptococcal nonsuppurative complications to be found.

#### COMMENT

The results of this study are of course not altogether objective. The severity of the disease in individual patients varied to some extent, and although every attempt was made to apply different schedules to patients with comparable illness, this was not always possible. Some of the groups were small, especially when the results obtained from the first few patients treated with a given schedule were unsatisfactory.

TABLE 2.—*Time-Dose Relationship in Penicillin Schedules for the Treatment of Streptococcal Sore Throat (Individual Dose and Interval Fixed, Total Length of Treatment Varied)*

Schedule	No. of Days Treated	No. of Patients	Clinical Response	No. of Clinical Relapses	No. of Bacterio- logic Relapses	Result
150,000 units every 12 hr. $\times$ 4	2	12	Excellent	5	9	Unsatisfactory
150,000 units every 12 hr. $\times$ 6	3	14	Excellent	2	7	Unsatisfactory
150,000 units every 12 hr. $\times$ 8	4	12	Excellent	0	1	Satisfactory

It seems justifiable, however, to draw the following conclusions from the data at hand:

1. If doses are plotted on a logarithmical scale against the intervals between injections (chart) the satisfactory results seem to be grouped along a straight line, suggesting that the time-dose relationship obtained for experimental animals with multiple injections may hold true in human streptococcal disease.

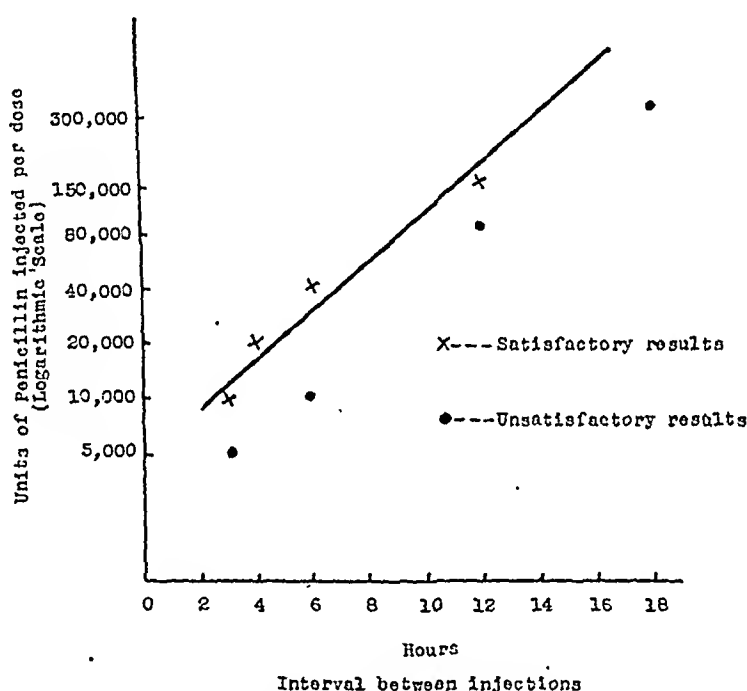
2. Since some of the large dose, long interval schedules gave satisfactory results it must be accepted that blood levels of penicillin are not essential for the satisfactory treatment of all bacterial infections responding to this drug.<sup>7</sup> Apparently high peaks of penicillin in the tissues may so influence bacterial populations as to inhibit growth for a significant length of time. This has been actually demonstrated by bacteriologic methods in experimental animals<sup>3</sup> and may apply to human streptococcal diseases as well as to other infections.<sup>4</sup>

3. The interval between large doses can probably be extended only to certain limits. These limits are most likely set not by penicillin

<sup>7</sup> Intramuscular injection of 150,000 units of penicillin in isotonic sodium chloride produces measurable blood levels for about five to seven hours (Ory, E. M.; Wilcox, C., and Finland, M.: Serum Levels After Repository Injections of Penicillin, *Proc. Soc. Exper. Biol. & Med.* 62:86, 1946).

blood levels but rather by the escape of the bacterial population from the depressant effect of high penicillin peaks. Evidence for this statement is entirely derived from animal experimentation. In at least one human disease, syphilis, similar observations have been recorded by Shaffer.<sup>8</sup> He obtained apparently satisfactory results in a significant proportion of patients treated with only two weekly injections of 600,000 units of penicillin in beeswax and peanut oil for eight weeks. From all available evidence these patients must have lacked measurable blood levels during at least one half of the total period of the penicillin treatment.

In experimental animals it is possible to cure both syphilis and streptococcal disease with a single large injection of aqueous penicillin.



Relationship of the individual dose of penicillin to the time interval between injections.

Similar single injections in human beings would require doses far in excess of the scope of this work. Such "therapia sterilizans magna" has been accomplished with aqueous penicillin in human gonorrhea.<sup>9</sup> It may be stated that treatments with single doses or large dose, long interval schedules are wasteful and are probably of more theoretic than practical importance. Intermediate schedules, however, utilizing six to eight hour intervals, may be applicable occasionally for hospitalized patients

8. Shaffer, L. W.: Outpatient Administration of P. O. B., in Thirteenth Venereal Disease Control Seminar, San Francisco, May 26, 1947.

9. Welch, H.; Putnam, L. E.; Randall, W. A., and Herwick, R. P.: Penicillin X: Successful Treatment of Gonorrhea with a Single Intramuscular Injection, J. A. M. A. 126:1024 (Dec. 16) 1944.

whom one wishes to spare the discomfort and risk of allergic reaction from penicillin in peanut oil and beeswax. In the great majority of other infections they have not succeeded to date, perhaps partly because only doses of insufficient magnitude were used.

#### SUMMARY

Eighty-one patients with streptococcic sore throat were treated with various experimental penicillin schedules. Equally satisfactory results could be obtained with small doses injected frequently as with large doses given up to twelve hours apart provided treatment was continued for four days. In order to permit a twofold increase in the interval between injections the dose of penicillin had to be increased fourfold. Excellent results could be obtained even if measurable blood levels were absent for about half of the period of treatment.

Members of the staff of the United States Marine Hospital cooperated in this study by furnishing suitable patients with streptococcic sore throat.

National Institute of Health.

# Progress in Internal Medicine

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## CARDIOVASCULAR DISEASES

A Review of Significant Publications From January 1944 to June 1947

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**I**N A REVIEW covering a three and one-half year period one cannot completely appraise all the interesting and significant papers which have appeared since December 1943. A detailed report of the investigations in the field of cardiovascular disease during this interval would comprise an extensive volume. It has therefore been necessary, in order to achieve reasonable brevity, to stress only those aspects of the subject which represent the most original contributions to the field and which in our opinion hold the greatest promise for the future.

### ANATOMIC AND PHYSIOLOGIC ASPECTS

The traditional concepts of the structure and functions of the conducting tissues of the heart have recently been subjected to a critical review by the Glomsets and Birge.<sup>1</sup> Being unable to convince themselves of the existence of a special muscular conducting bundle in the dog or in man, they surveyed the literature to see if the experience of others justified the belief that bundle branch block was due to blocking lesions in branches of a special conducting system. These authors point out that Keith and Flack, Tawara, Moenckeberg and many others described the His bundle in man as visible to the naked eye but that more recently some workers have believed that the conducting tissue cannot be identified without serial sections. Their own observations lead them to the conclusion that the bundle in question is indistinguishable from other muscle fasciculi. They point out that blocking lesions have not been consistently described with bundle branch block and that they have not invariably been found on the side which one would expect

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1. Glomset, D. J.; Glomset, A. T. A., and Birge, R. F.: Morphologic Study of the Cardiac Conduction System: III. Bundle Branch Block, *Am. Heart J.* **28**:348, 1944. Glomset, D. J., and Birge, R. F.: Morphologic Study of the Cardiac Conduction System: IV. The Anatomy of the Upper Part of the Ventricular Septum in Man, *ibid.* **29**:526, 1945.

(Yater<sup>2</sup> noted in 1938, however, that bundle branch block is usually associated with bilateral bundle branch lesions, although one branch was usually more seriously affected than the other.) This heretical approach is capped by the statements that "the evidence presented to prove the existence of a special conducting system is irrelevant and immaterial" and "we have found no anatomic evidence to support the myogenic theory of cardiac conduction." Such assertions, while refreshing in their frankness, must await critical review by those relatively few histologists and pathologists who are competent in this difficult field.

Studies on the collateral circulation of the normal human heart have been undertaken by Prinzmetal and his co-workers,<sup>3</sup> who employed coronary perfusion with radioactive erythrocytes and with glass spheres. They state that they have demonstrated intercoronary anastomoses of arteriolar dimensions, large arteriovenous anastomoses (140 microns) and large communications between the coronary arteries and the ventricular cavities.

Gregg<sup>4</sup> has published a critique of certain of the experimental studies performed in the past which attempted to demonstrate the dynamics of the coronary circulation. It is his contention that many of the previously reported observations were made under grossly abnormal conditions, such as artificial respiration with open thorax, the use of the heart-lung preparation and the employment of coronary perfusion. He also questions the dependability of certain of the measuring devices on which experimental results have been based. In an attempt to conduct experiments which would adopt some of Gregg's suggestions, Eckenhoff and his associates<sup>5</sup> studied the coronary circulation in dogs, which although anesthetized and heparinized had in most instances a closed thorax and spontaneous breathing. They used a bubble flow meter to measure the coronary circulation and injected terminally Evans blue dye through the cannula in the coronary artery to determine the flow per gram of heart tissue. The important observation (made previously by other workers) that the coronary flow varied directly with cardiac rate and also with blood pressure was confirmed. Unlike other workers in the field, however, they were not able to demonstrate significant coronary vasoconstrictor activity on stimulation of the vagus or

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2. Yater, W. M.: Pathogenesis of Bundle Branch Block, Review of Literature; Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of Conduction System, *Arch. Int. Med.* **62**:1 (July) 1938.

3. Prinzmetal, M.; Simkin, B.; Bergman, H. C., and Kruger, H. E.: Studies on the Coronary Circulation: II. The Collateral Circulation of the Normal Human Heart by Coronary Perfusion with Radioactive Erythrocytes and Glass Spheres, *Am. Heart J.* **33**:420, 1947.

4. Gregg, D. E.: The Coronary Circulation, *Physiol. Rev.* **26**:28, 1946.

5. Eckenhoff, J. E.; Hafkenschiel, J. H., and Landmesser, C. M.: The Coronary Circulation in the Dog, *Am. J. Physiol.* **148**:582, 1947.

accelerator nerves and were not able to find reflex vasoconstriction in the other coronary arteries after one artery had been ligated. Furthermore, they were unable to demonstrate any change in the coronary blood flow when the gallbladder was distended beyond that which could be attributed to change in blood pressure. Both epinephrine and acetylcholine when injected into a coronary artery increased the amount of flow, and the presence of anoxia was also found to be a potent coronary dilator. It appeared that under standard conditions the dog's heart received about 5 per cent of the total cardiac output but that as the output of the heart decreased the percentage of blood delivered to the coronary circulation rose; however, as the output fell the actual flow per hundred grams of heart tissue decreased. Eckenhoff and his collaborators<sup>6</sup> concluded from further experiments, also conducted on dogs, that cardiac efficiency tends to vary directly with cardiac output and inversely with arterial blood pressure.

The technic of catheterization of the right side of the heart has permitted measurements of the cardiac output in man by the direct Fick principle. This method requires estimates of the oxygen or carbon dioxide content of arterial blood obtained from the femoral artery and of mixed venous blood obtained from the right side of the heart as well as of the total oxygen intake or carbon dioxide elimination by the lungs per unit of time. Cournand and his colleagues<sup>7</sup> have found an average cardiac index (cardiac output in liters per minute per square meter of body surface) of 3.12 in 13 normal males. This figure is 26 per cent higher than the average obtained by either the ethyl iodide or the acetylene method for a similar group. In England, McMichael and Sharpey-Schafer<sup>8</sup> with the same technic have found that the cardiac output increased by an average of 33 per cent when normal subjects changed from the erect to the supine position. They noted that a reduction in the right auricular pressure produced a fall in the cardiac output whereas a rise in this pressure brought about a rise in the output. It was of interest that small doses of epinephrine, which were without effect on cardiac rate or blood pressure, resulted in an increase in the cardiac output; this phenomenon is due, they believe, to an increase in systolic ejection by the ventricles. Their

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6. Eckenhoff, J. E.; Hafkenschiel, J. H.; Landmesser, C. M., and Harmel, M.: Cardiac Oxygen Metabolism and Control of the Coronary Circulation, *Am. J. Physiol.* **149**:634, 1947.

7. Cournand, A.; Riley, R. R.; Breed, E. S.; Baldwin, E. de F., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, *J. Clin. Investigation* **24**: 106, 1945.

8. McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output in Man by a Direct Fick Method, *Brit. Heart J.* **6**:33, 1944.



work and that of others on the dynamics of the systemic circulation in man have been summarized in a recent paper by Richards.<sup>9</sup>

The presence of multiple arteriovenous fistulas on the left forearm of a 19 year old youth gave Kennedy and Burwell<sup>10</sup> an opportunity to study the effects of such vascular shunts on the circulation. Their results indicated a definite rise in blood volume and in cardiac output, the work of the heart being increased approximately 25 per cent. Brannon, Merrill, Warren and Stead<sup>11</sup> have determined the cardiac output in patients whose hemoglobin level was below 7 Gm. per hundred cubic centimeters. These authors observed that with anemia of such a degree the cardiac output was increased when the patients were at rest and the arteriovenous oxygen difference and the peripheral resistance were decreased.

The effect of obstruction to the superior vena cava on respiration and circulation has been made the basis of a report by Altschule, Iglauer and Zamcheck.<sup>12</sup> They observed 5 male patients with this syndrome and found an increase in the respiratory rate, an increase in the respiratory volume and a reduced amount of carbon dioxide in the alveolar air (in comparison with the findings when the respiratory symptoms had disappeared either spontaneously or as a result of treatment). In addition they learned that the arteriovenous oxygen difference in this condition was increased in the upper extremities but was normal in the legs. They agree with other writers that hyperventilation and dyspnea are commonly found with this syndrome and may be caused by a slowed blood flow with stasis in the region of the respiratory center. In summary they say: "A corollary to the foregoing conclusion is that cerebral stasis is a cause of hyperventilation and dyspnea in cardiac decompensation . . . it is not to be concluded, however, that congestion of the lungs may be minimized as a factor in the symptoms of cardiac decompensation."

#### HEART FAILURE: PHYSIOLOGIC ASPECTS AND TREATMENT

Considerable controversy regarding fluid dynamics and the role of the heart in chronic congestive heart failure has resulted from the work

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9. Richards, D. W.: Observations on the Dynamics of the Systemic Circulation in Man, *Bull. New York Acad. Med.* **22**:630, 1946.

10. Kennedy, J. A., and Burwell, C. S.: Measurements of the Circulation in a Patient with Multiple Arteriovenous Connections, *Am. Heart J.* **28**:133, 1944.

11. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia, as Measured by the Technique of Right Atrial Catheterization, *J. Clin. Investigation* **24**:332, 1945.

12. Altschule, M. D.; Iglauer, A., and Zamcheck, N.: Respiration and Circulation in Patients with Obstruction of the Superior Vena Cava: Cerebral Factors in Dyspnea and Orthopnea, *Arch. Int. Med.* **75**:24 (Jan.) 1945.

of Warren and Stead.<sup>13</sup> These authors noted in 2 patients that an accumulation of extracellular fluid as evidenced by increase in weight occurred in congestive failure before any increase in venous pressure could be demonstrated. Associated with this phenomenon was a proportionate increase in blood volume. They consider this accumulation of extracellular fluid to be essentially an increase of sodium chloride in water resulting in all probability because the kidneys, when impaired cardiac function is present, do not excrete salt, and thus water, normally. The resultant increase in blood volume, which they believe to be one manifestation of the increase in amount and pressure of the extracellular fluid, results in turn in an increase in venous pressure. However, they also mention local increases in venous pressure as important factors in formation of edema in certain areas such as the lungs, where there may be a discrepancy between the output from the right and that from the left ventricle, and the limbs, where the factor of gravity is important.

Acute heart failure they consider a different situation, analogous to cardiac tamponade and to an increase in vascular tone and not related to an increase in plasma volume.

In confirmation of this theory is Merrill's<sup>14</sup> study of a group of patients with chronic congestive heart failure (excluding those with obvious associated renal disease) in whom he found that the renal plasma flow was reduced to one third or less of the normal amount and that the renal filtration fraction was also subnormal. He believes that retention of sodium is caused by the low filtration rate and not by increased reabsorption of salt. Merrill noted that the blood flow through the kidneys was reduced to one fifth of the normal figure when the cardiac output was approximately one half the normal amount, which indicated a specific diversion of blood away from the kidneys which might be further exaggerated during exercise. He concludes that the reduction in renal blood flow bears no relation to venous pressure but is correlated with the reduced cardiac output—an indication that it is a "forward failure" phenomenon.

These views have not gone uncontested. Landis<sup>15</sup> has contrasted the theory held by Warren and Stead with that proposed many years

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13. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure: Interpretation of Mechanisms Producing Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients with Prolonged Congestive Failure, *Arch. Int. Med.* **73**:138 (Feb.) 1944.

14. Merrill, A. J.: Edema and Decreased Renal Blood Flow in Patients with Chronic Congestive Heart Failure: Evidence of "Forward Failure" as the Primary Cause of Edema, *J. Clin. Investigation* **25**:389, 1946.

15. Landis, E. M.; Brown, E.; Fauteux, M., and Wise, C.: Central Venous Pressure in Relation to Cardiac "Competence," Blood Volume, and Exercise, *J. Clin. Investigation* **25**:237, 1946.

ago by Starling, who had suggested that the sequence in chronic congestive failure was that of cardiac failure, elevated venous pressure, accumulation of blood in the large veins, compensatory arteriolar constriction, bone marrow anoxia and an increase in blood volume. Landis and his colleagues have considered muscular activity important as a factor in the elevation of venous pressure (the conclusions of Warren and Stead were drawn from observations on patients in the resting state only). Using dogs for their experimental work, they found that in normal animals the venous pressure recorded from the superior vena cava tended to fall during graded exercise but that exercise in animals with myocardial damage (resulting from ligation of the coronary artery), auricular fibrillation or cardiac tamponade was associated with either an actual elevation of venous pressure or a less striking decrease than that in normal animals. The conclusion from their observations was that this actual or relative increase in venous pressure was not due to the presence of tachycardia. These workers also doubted that a simple increase in blood volume would elevate the central venous pressure in a normal animal at rest or during activity, and as a result of experiments in which large amounts of blood were rapidly transfused into the circulation of test dogs they concluded that such a rise in venous pressure was virtually impossible. It is their opinion that the intermittent relative or absolute increase in venous pressure during exercise is due to the inability of a heart with reduced "competence" to cope with the increased venous return consequent to muscular activity. Secondary to this increase in pressure is the temporary sequestration of blood in the venous system, accompanied with excessive filtration of fluid, with resulting reduction of circulating blood volume, compensatory vasoconstriction and subsequent plethora. The elevated venous pressure occurring in a person at rest with chronic congestive failure may thus be due to faulty cardiac "competence," plus the additional burden of increase in plasma volume.

Another criticism of the views of Warren and Stead comes from Reichsman and Grant.<sup>16</sup> These workers followed the course of 3 patients in whom cardiac decompensation developed after digitalis had been withheld. Their charts indicate that in the 3 cases the venous pressure rose before the body weight became increased. They suggest that initial dehydration may have precipitated the early gain in weight in at least 1 of the patients studied by Warren and Stead. The result of these and other investigations has been a renewed and healthy interest in the pathologic changes in heart failure.

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16. Reichsman, F., and Grant, H.: Some Observations on the Pathogenesis of Edema in Cardiac Failure, *Am. Heart J.* 32:438, 1946.

A less complex aspect of the problem has been studied by Nylin,<sup>17</sup> who used red blood corpuscles labeled with radioactive phosphorus to determine the circulating blood volume. Observations made on 2 patients with heart failure revealed a considerable increase both in the number of blood corpuscles and in the circulating blood volume. One of the patients was followed after the evidences of cardiac failure had disappeared, and it was found that both the blood volume and the quantity of corpuscles had decreased. Perera,<sup>18</sup> working at the Presbyterian Hospital in New York, was interested in comparing the increase in plasma volume during predominant cardiac insufficiency on the right side with the size of the liver. It appears from his observations, necessarily gross, that there is a direct relation between the two, and he refers to the possibility that the increase in plasma volume is due to dilatation and engorgement of vascular channels in the liver and in the portal circulatory beds. Work on plasma volume has also been conducted by Lyons, Jacobson and Avery,<sup>19</sup> who have demonstrated in normal subjects increased volume after a large intake of sodium salts in association with slight gain in weight and an elevation of peripheral venous pressure. They suggest that an increase in the amount of extracellular fluid along the course of the peripheral veins may produce a rise in tissue tone, partial obstruction of the vein and in turn an elevation of the venous pressure level.

The effects of a subtropical climate on patients with congestive heart failure have been investigated by Burch.<sup>20</sup> He found that the rate of water loss from the skin of these patients is markedly lowered when severe congestion is present and that as the signs of failure subside the rate of water loss returns to a more normal level. He also observed that the rates of water and heat loss from the respiratory tract of 24 patients with heart failure involving both ventricles are definitely greater than the rates observed under similar conditions in 107 normal subjects.

Altschule and Zamcheck<sup>21</sup> undertook studies on 8 patients with pleural effusions, 4 of whom were suffering from heart disease with

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17. Nylin, G.: Blood Volume Changes with Radioactive Phosphorus, *Brit. Heart J.* **7**:81, 1945.

18. Perera, G. A.: The Increased Plasma Volume in Cardiac Insufficiency: Its Correlation with Right-Sided Failure, *J. Clin. Investigation* **24**:708, 1945.

19. Lyons, R. H.; Jacobson, S. D., and Avery, N. L.: Increases in the Plasma Volume Following the Administration of Sodium Salts, *Am. J. M. Sc.* **208**: 148, 1944.

20. Burch, G. E.: Congestive Heart Failure in a Subtropical Climate, *Am. J. M. Sc.* **211**:181, 1946; The Rates of Water and Heat Loss from the Respiratory Tract of Patients with Congestive Heart Failure Who Were from a Subtropical Climate and Resting in a Comfortable Atmosphere, *Am. Heart J.* **32**:88, 1946.

21. Altschule, M. D., and Zamcheck, N.: The Effects of Pleural Effusion on Respiration and Circulation in Man, *J. Clin. Investigation* **23**:325, 1944.

congestive failure. They found that after thoracentesis there was an increase in the functional, residual and reserve air and that the venous pressure fell significantly whether or not the original pressure was normal. It was their impression that the existence of a pleural effusion is not per se a factor which impairs the cardiac output in patients at rest. The preponderance of hydrothorax of the right side in congestive heart failure has been the subject of a report by McPeak and Levine,<sup>22</sup> who wished to check the accuracy of statements by other authors to the effect that hydrothorax of the left side is common in hypertensive heart disease with congestion and in other types of left ventricular failure. It was the conclusion of McPeak and Levine that hydrothorax of the right side predominates in 56 to 80 per cent of patients with congestion on a cardiac basis, regardless of the nature of the underlying condition.

From England has come a most interesting description of the occurrence of heart failure in patients with osteitis deformans (Paget's disease). Edholm, Howarth and McMichael<sup>23</sup> discovered that the extensive vascularity of the bones affected by this disease results essentially in an arteriovenous shunt, the effect of which is to produce strain on the heart and in certain cases actual cardiac failure such as occurs in other types of arteriovenous fistulas. With the use of tourniquets which isolated the circulation of the affected limbs, they were able to lower the heart rate, cardiac output and right auricular pressure and to elevate slightly the diastolic pressure. Their observations draw attention to this additional condition which must be considered in the differential diagnosis for patients with congestive heart failure of obscure origin. Obviously such a possibility is especially to be explored in dealing with older persons.

The mechanism of prolonged circulation time associated with myocardial insufficiency was investigated by Nylin,<sup>24</sup> who used red blood corpuscles labeled with radioactive phosphorus. He determined, by means of a Geiger counter, the activity of fractioned specimens of arterial blood from normal subjects and from patients with large hearts, obtaining for the former a dilution curve characterized by a sharp rise and fall and for the latter group a much more gradual ascent and descent. As a result of these researches Nylin believes that the prolongation of the circulation time in patients with large hearts is probably not due to stasis alone but is perhaps chiefly related to cardiac dilatation and thus to the amount of residual blood in the cavities of the heart.

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22. McPeak, E. M., and Levine, S. A.: Preponderance of Right Hydrothorax in Congestive Heart Failure, *Ann. Int. Med.* **25**:916, 1946.

23. Edholm, O. G.; Howarth, S. M., and McMichael, J.: Heart Failure and Bone Blood Flow in Osteitis Deformans, *Clin. Sc.* **5**:249, 1945.

24. Nylin, G.: The Dilution Curve of Activity in Arterial Blood After Intravenous Injection of Labeled Corpuscles, *Am. Heart J.* **30**:1, 1945.

Although the importance of low sodium intake for patients with reduced myocardial reserve has been the topic of several publications over the past forty years, it is only recently that adequate emphasis has been placed on this important aspect of the therapy of heart failure. The reports of Schemm<sup>25</sup> publicized his successes in the management of edema by the use of a high fluid and low sodium intake combined with a neutral or acid ash diet. More recently it has appeared from the work of others, including Bridges, Wheeler and White<sup>26</sup> as well as Leevy and his associates,<sup>27</sup> that the most important requirement for success with this regimen is a rigid restriction of sodium intake. It is doubtful that it is wise or desirable to force fluids, and it also appears unnecessary to insist on an intake of acid ash food. The group at the Massachusetts General Hospital found that a sodium intake of around 600 mg. can be maintained by most hospitalized and ambulatory patients without undue difficulty and that such a measure may control edema which has previously been resistant in addition to reducing the need for mercurial diuretics. However, like the rice diet which will be described later, such a routine is not without its drawbacks: Many persons suffer considerable initial mental distress when salt is removed from their diet, and patients who must exist on restaurant fare may find it impossible to restrict properly their intake of salt. At times an overvigorous diuresis of sodium may occur in persons on this diet who are receiving mercurial diuretics, with resulting muscular cramps and even vomiting. Such symptoms are easily controlled, however, with a little added salt. These authors stress how necessary it is not only to restrict the intake of sodium chloride but also to eliminate the use of all types of alkaline drugs which contain significant amounts of sodium ion.

Just as attention is now being directed to early mobilization in surgical patients, so also is the harmful effect of recumbency in the treatment of heart disease the subject of recent papers. Levine<sup>28</sup> points out that the patient himself seeks relief from nocturnal dyspnea by assuming the sitting or erect position. He states that lung volume and vital capacity also tend to decrease with recumbency, and he urges that rest in bed should not be employed to a degree which is

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25. Schemm, F. R.: A High Fluid Intake in the Management of Edema, Especially Cardiac Edema: II. Clinical Observations and Data, *Ann. Int. Med.* **21**:937, 1944.

26. Bridges, W. C.; Wheeler, E. O., and White, P. D.: Low Sodium Diet and Free Fluid Intake in the Treatment of Congestive Failure, *New England J. Med.* **234**:573, 1946. Wheeler, E. O.; Bridges, W. C., and White, P. D.: Diet Low in Salt (Sodium) in Congestive Heart Failure, *J.A.M.A.* **133**:16 (Jan. 4) 1947.

27. Leevy, C. M.; Strazza, J. A., and Jaffin, A. E.: Fluids in Congestive Heart Failure, *J.A.M.A.* **131**:1120 (Aug. 3) 1946.

28. Levine, S. A.: Some Harmful Effects of Recumbency in the Treatment of Heart Disease, *J.A.M.A.* **126**:80 (Sept. 9) 1944.

actually deleterious to the patient's condition. Wheeler and White<sup>29</sup> have pointed out in this regard that insomnia may for a time appear as the only symptom of pulmonary congestion accompanying nocturnal recumbency and that it will respond dramatically to the use of diuretics. Harrison<sup>30</sup> holds views similar to those of Levine and advises early ambulation in cases of congestive heart failure as soon as severe dyspnea has subsided. He suggested the observance of the sensible rule that in severe heart disease activity should be kept below the symptomatic threshold.

#### CONGENITAL HEART DISEASE

Great strides continue to be made in the diagnosis and treatment of congenital cardiovascular defects. Using the technic of catheterization of the right side of the heart, Cournand,<sup>7</sup> Sosman and Dexter,<sup>31</sup> Brannon and associates<sup>32</sup> and others have obtained valuable information regarding the pressures in the right auricle and ventricle as well as in the pulmonary arteries, have been able to estimate the cardiac output and study the oxygen saturation of the aforementioned areas, have found certain characteristic pressure curves for individual conditions and have at times directly indicated the presence of septal or other defects by the course which the catheter has taken. It would appear that we are just beginning to tap the information which may be obtained through this technic. (The details of this new diagnostic method are not suitable for inclusion in a review of this type, but a complete description can be found in the references just mentioned.)

Porter<sup>33</sup> has described an interesting set of twins, 1 of whom was found to have a patent ductus arteriosus. This twin was shorter and lighter than his brother, but after ligation of the ductus he outgrew him although he still weighed somewhat less. The author also refers to 2 other patients with patent ductus arteriosus who were smaller and less heavy than other members of their respective families. The clinical features of 37 cases of patent ductus arteriosus proved at

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29. Wheeler, E. O., and White, P. D.: Insomnia Due to Left Ventricular Heart Failure Unrecognized as Such and Inadequately Treated, *J.A.M.A.* **129**: 1158 (Dec. 22) 1945.

30. Harrison, T. R.: Abuse of Rest as a Therapeutic Measure for Patients with Cardiovascular Disease, *J. A. M. A.* **125**:1075 (Aug. 19) 1944.

31. Sosman, M. C.: Venous Catheterization of the Heart: I. Indications, Technics, and Errors, *Radiology* **48**:441, 1947. Dexter, L.: Venous Catheterization of the Heart: II. Results, Interpretations, and Value, *ibid.* **48**:451, 1947.

32. Brannon, E. S.; Weens, H. S., and Warren, J. V.: Atrial Septal Defect: Study of Hemodynamics by the Technique of Right Heart Catheterization, *Am. J. M. Sc.* **210**:480, 1945.

33. Porter, W. B.: The Effect of Patent Ductus Arteriosus on Body Growth, *Am. J. M. Sc.* **213**:178, 1947.

operation have been reviewed by Levine and Geremia.<sup>34</sup> They observed that the systolic phase of the murmur was never less than grade II, that a diastolic phase was always present, that an apical systolic murmur could invariably be heard and that 4 of their 37 patients also had an apical mid-diastolic rumble. Occasionally a slight pulmonic systolic murmur persisted after operation; there was only 1 instance of a persistent diastolic murmur (the patient was found to have subacute bacterial endocarditis involving his aortic valve).

It is to be regretted that the numerous reports regarding the incidence of congenital anomalies following maternal rubella in the early weeks of pregnancy do not give more precise information as to the exact types of cardiac defects. For example, Albaugh,<sup>35</sup> in his description of 9 infants with such anomalies, states that 8 of them had "heart lesions" but gives no further details, nor does a recent review of this problem by Wesselhoeft<sup>36</sup> throw further light on the nature of the cardiac changes although it presents an excellent statement of the facts at hand. It is to be hoped that more complete reports will be available soon.

Ligation or division of the patent ductus arteriosus has gained a deserved increasing popularity. Gross and Ware<sup>37</sup> have reported a series of 130 cases in which they operated, with a mortality of only 3.8 per cent. They advise that operation be done preferably during childhood. While it is Gross's present opinion<sup>38</sup> that surgical division of the ductus is preferable to ligation alone because the latter technic has in certain instances been followed by persistence or reopening of the arteriovenous shunt, Blalock<sup>39</sup> considers division to be not only unnecessary but even unwise. He recommends the use of purse-string sutures at the extreme ends of the ductus followed by two through and through mattress sutures plus a ligature of umbilical tape.

Coarctation of the aorta, a condition which has recently been reviewed excellently by Reifenstein, Levine and Gross,<sup>40</sup> also is being approached

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34. Levine, S. A., and Geremia, A. E.: Clinical Features of Patent Ductus Arteriosus with Special Reference to Cardiac Murmurs, *Am. J. M. Sc.* **213**: 385, 1947.

35. Albaugh, C. H.: Congenital Anomalies Following Maternal Rubella in Early Weeks of Pregnancy, with Special Emphasis on Congenital Cataract, *J.A.M.A.* **129**:719 (Nov. 10) 1945.

36. Wesselhoeft, C.: Medical Progress: Rubella, *New England J. Med.* **236**: 943 and 978, 1947.

37. Gross, R. E., and Ware, P. F.: The Surgical Significance of Aortic Arch Anomalies, *Surg., Gynec. & Obst.* **83**:435, 1946.

38. Gross, R. E.: Complete Surgical Division of the Patent Ductus Arteriosus, *Surg., Gynec. & Obst.* **78**:36, 1944.

39. Blalock, A.: Operative Closure of the Patent Ductus Arteriosus, *Surg., Gynec. & Obst.* **82**:113, 1946.

40. Reifenstein, G. H.; Levine, S. A., and Gross, R. E.: Coarctation of the Aorta, *Am. Heart J.* **33**:146, 1947.



surgically without trepidation in certain clinics. Crafoord and Nylin,<sup>41</sup> of Stockholm, had observed in the past that clamping of the aorta during an operation on a patent ductus arteriosus produced no untoward effects. Encouraged by this helpful information, Crafoord in October 1944 for the first time resected the coarcted portion of an aorta and performed an end to end anastomosis of the proximal and distal aortic segments. These authors found that a gratifying drop in blood pressure took place in the arms postoperatively, along with an increase in the oscillations and blood pressure in the legs. Shortly after this Gross and Hufnagel<sup>42</sup> described experimental work in which a similar direct aortic anastomosis was employed in dogs and also reported the results of operation on 2 patients, 1 of whom died when the aortic clamps were suddenly released. More recently, Gross<sup>43</sup> has operated on 28 additional patients, with encouraging results. It is to be hoped that the life span of patients with this type of congenital cardiac disease may be prolonged by the introduction of this new surgical treatment.

Even more dramatic has been the work of Taussig and Blalock,<sup>44</sup> who have approached the problem of tetralogy of Fallot with a view toward increasing the volume of the pulmonary circulation and thus increasing the degree of arterial oxygen saturation and lessening cyanosis and polycythemia. Employing the technic of end to side anastomosis of one subclavian or innominate artery to a pulmonary artery on the same side, they have been able in most instances to attain an arterial oxygen saturation level of between 75 and 88 per cent and definitely to improve the condition of their patients and their tolerance to exercise. Blalock's series now comprises more than 509 cases,<sup>45</sup> with an over-all mortality of 18 per cent. In an earlier group of 110 cases, in which he had reported a mortality of 23 per cent, all but 1 of the surviving patients showed clinical improvement. In Chicago, Potts and his associates<sup>46</sup> have

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41. Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, *J. Thoracic Surg.* **14**:347, 1945.

42. Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta, *New England J. Med.* **233**:287, 1945.

43. Gross, R. E.: Personal communication to the authors. Gross and Ware.<sup>37</sup>

44. Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, *J.A.M.A.* **128**:189 (May 19) 1945. Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardio-Vascular Defects, *Bull. New York Acad. Med.* **22**:57, 1946; The Surgical Treatment of Congenital Pulmonic Stenosis, *Ann. Surg.* **124**:879, 1946. Taussig, H. B., and Blalock, A.: Observations on the Volume of the Pulmonary Circulation and Its Importance in the Production of Cyanosis and Polycythemia, *Am. Heart J.* **33**:413, 1947.

45. Blalock, A.: Personal communication to the authors.

46. Potts, W. J.; Smith, S., and Gibson, S.: Anastomosis of the Aorta to a Pulmonary Artery: Certain Types in Congenital Heart Disease, *J.A.M.A.* **132**: 627 (Nov. 16) 1946. Potts, W. J.: Personal communication to the authors.

used a different technic involving a direct side to side anastomosis between the left pulmonary artery and the aorta by means of a special aortic clamp which they devised. Such a procedure has the advantage of sparing the subclavian and innominate arteries, one of which must be sacrificed if the Blalock method is used. These authors have performed their operation on 45 patients with tetralogy of Fallot and have reported only 4 deaths.

The significance of anomalies of the aortic arch in the production of tracheal and esophageal obstruction has been recognized only recently,<sup>47</sup> and with this recognition has come the use of surgical intervention. Gross and Ware<sup>37</sup> have operated on 3 patients with vascular rings, and Sweet, Findlay and Reyersbach<sup>48</sup> have reported operation on 2 others. Both sets of workers have been able to relieve the obstruction by the division of one or more anomalous vessels. It is too early for a report on an adequate follow-up of these cases, but the new form of treatment may prevent the serious pulmonary complications which sometimes result if this condition is allowed to persist over a long period.

Mention should also be made of an experimental method for the production and subsequent closure of interauricular septal defects proposed by Cohn.<sup>49</sup> This enthusiastic worker sutured a portion of the right auricle over experimentally produced auricular septal defects in dogs, securing in most cases satisfactory closure. It would appear that soon there may be no portion of the heart which is not accessible to the surgeon's knife.

#### RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

A series of articles by Rantz, Boisvert and Spink<sup>50</sup> has provided further data on the relationship between streptococcic infections and rheumatic fever. Using the large volume of clinical material available in an army installation, these authors discovered 15 cases of rheumatic fever among a series of 410 patients known to have had respiratory infections caused by group A hemolytic streptococci. In another series

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47. Faber, H. K.; Hope, J. W., and Robinson, F. L.: Chronic Stridor in Early Life Due to Persistent Right Aortic Arch, *J. Pediat.* **26**:128, 1945.

48. Sweet, R. H.; Findlay, C. W., Jr., and Reyersbach, G. C.: The Diagnosis and Treatment of Tracheal and Esophageal Obstruction Due to Congenital Vascular Ring, *J. Pediat.* **30**:1, 1947.

49. Cohn, R.: An Experimental Method for the Closure of Interauricular Septal Defects in Dogs, *Am. Heart J.* **33**:453, 1947.

50. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, *Arch. Int. Med.* **76**:131 (Sept.) 1945. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat, *ibid.* **77**:66 (Jan.) 1946. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat, *ibid.* **79**:401 (April) 1947.

of 871 patients with respiratory diseases definitely not due to group A hemolytic streptococci there were no instances of rheumatic fever. It is of interest that many of their patients had a period of vague ill health after the original bacterial infection before rheumatism could be diagnosed. They suggest that repeated infections with different types of hemolytic streptococci may be necessary to produce the active rheumatic state (implying a tissue sensitivity to a fraction or product common to all types of hemolytic streptococci belonging to group A). In this regard the authors observed rheumatic fever to be twice as common among a small group of patients who became reinfected with different types of streptococci two to three weeks after the initial illness as among a larger group infected with only one strain. They also noted abnormalities similar to those found with active rheumatic fever in the electrocardiograms made on patients who had been hospitalized for hemolytic streptococcic sore throat but in whom typical rheumatic fever had never developed otherwise. However, it should be pointed out that the sedimentation rate was invariably elevated in this group of patients. The authors consider the varied clinical and laboratory abnormalities which may occur after hemolytic streptococcic sore throat, believe them all to be manifestations of the same pathologic process and advise that they be grouped together as phases of the "post-streptococcic state." Similar conclusions were reached by Watson, Rothbard and Swift<sup>51</sup> in a review of 110 cases of scarlet fever in young adults.

Cardiac lesions of the rheumatic type have been reported by Rich and Gregory<sup>52</sup> to have been produced in rabbits by the serum sickness type of anaphylactic reaction after the intravenous injection of foreign protein material. They have described lesions of the heart valves, endocardium, myocardium and pericardium having characteristic Aschoff bodies. They have also pointed out the similarity between rheumatic fever and anaphylactic serum sickness in human beings and have described the similarity of rheumatic pneumonitis to the pneumonitis resulting from hypersensitivity to sulfonamide compounds. It is their belief that the lesions of rheumatic fever represent focal hypersensitivity reactions to a foreign antigen, perhaps a product of the hemolytic streptococcus. These workers have in addition described arterial lesions of the periarteritis nodosa type in animals subjected to hypersensitivity tests. Selye and his colleagues,<sup>53</sup> also using animal experimentation,

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51. Watson, R. F.; Rothbard, S., and Swift, H.: The Relationship of Post-scarlatinal Arthritis and Carditis to Rheumatic Fever, *J.A.M.A.* **128**:1145 (Aug. 18) 1945.

52. Rich, A. R., and Gregory, J. E.: Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity, *Bull. Johns Hopkins Hosp.* **75**:115, 1944.

53. Selye, H.; Sylvester, O.; Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, *J.A.M.A.* **124**:201 (Jan. 22) 1944.

reported the formation of Aschoff bodies in the myocardium as well as the presence of periarteritis nodosa in animals receiving large overdoses of desoxycorticosterone acetate. They found that unilateral nephrectomy and a high intake of sodium chloride facilitated these changes. Subsequently these authors took a series of rats, removed one kidney and either both adrenal glands or the thyroid gland and then administered large amounts of sodium chloride and desoxycorticosterone acetate. They believe that they have produced by this method a form of arthritis associated with histologic changes consistent with rheumatic fever. These studies open further avenues of investigation which may prove exceedingly far reaching.

The war era has resulted in numerous publications regarding the clinical characteristics of rheumatic fever encountered in the armed forces. Sokolow and Snell,<sup>54</sup> as well as many others, call attention to the atypical features which may be present with active rheumatic fever in young adults. The cerebral manifestations of this disease have been the subject of a paper by Warren and Chornyak,<sup>55</sup> who consider that 5 of their patients (among a series of 207) had evidences of intracranial involvement. In 1 of these the symptoms may have been attributable to salicylate intoxication; the other 4 patients showed, during the course of active rheumatic fever, a paranoid state (encountered twice), transient mental deterioration and loss of memory and ability to concentrate and partial paralysis of the left third nerve respectively.

Recurrence rates in rheumatic fever have been analyzed by Wilson and Lubschez.<sup>56</sup> They have shown that the risk of a major recurrence decreases with age and that this risk is greatest in the first year following an attack, becoming progressively less with the passage of time. Their statistics indicate that the risk of reactivity was not associated with the number of recurrences in the past, the presence of arthritis or chorea in previous attacks or the severity of the disease.

The thesis that early physical activity is of value in the treatment of active rheumatic fever has been expounded by Robertson, Schmidt and Feiring.<sup>57</sup> Using the patient's comfort as the single determining factor in prescribing strict rest in bed or physical activity, they believe that they have reduced the incidence of anxiety neurosis in 200 cases of the disease and at the same time obtained satisfactory clinical results.

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54. Sokolow, M., and Snell, A. M.: Atypical Features of Rheumatic Fever in Young Adults, *J.A.M.A.* **133**:981 (April 5) 1947.

55. Warren, H. A., and Chornyak, J.: Cerebral Manifestations of Acute Rheumatic Fever, *Arch. Int. Med.* **79**:589 (June) 1947.

56. Wilson, M. G., and Lubschez, R.: Recurrence Rates in Rheumatic Fever: Evaluation of Etiologic Concepts and Consequent Preventive Therapy, *J.A.M.A.* **126**:477 (Oct. 21) 1944.

57. Robertson, H. F.; Schmidt, R. E., and Feiring, W.: The Therapeutic Value of Early Physical Activity in Rheumatic Fever, *Am. J. M. Sc.* **211**:67, 1946.

This paper is open to the objection that there was not only incomplete reporting of the clinical and laboratory details of the cases in question but also a lack of control studies. Furthermore, the authors have no follow-up data available, and their experience was limited to the type of the disease affecting adults.

The treatment of the acute phase of rheumatic fever by large doses of salicylates has absorbed the attention of many writers. It is the conclusion of Manchester<sup>58</sup> that intensive treatment with salicylates, using the Coburn technic of intravenous administration, suppresses rheumatic infection in the acute phases, relieves articular and toxic manifestations, prevents significant cardiac damage and shortens the period of active infection. It is unfortunate that he fails to state the basis on which he selected his cases. Griffith<sup>59</sup> believes that large oral doses of sodium salicylate or acetylsalicylic acid with sodium bicarbonate are effective in the relief of pain and the lessening of fever and in aiding the absorption of transudates in serous cavities; he considers that the intravenous route is usually unnecessary. Taran<sup>60</sup> also states that massive doses of salicylates given orally are beneficial in rheumatic polyarthritides and carditis. A somewhat skeptical report comes from Warren, Higley and Coombs,<sup>61</sup> who found that while large doses of the drug were more effective in reducing pyrexia than small ones they nevertheless had no more effect on the sedimentation rate, did not reduce the occurrence of polycyclic attacks and did not prevent valvular disease. These authors did state, however, that large doses were more beneficial in the presence of acute pericarditis. Here again it would have been desirable to have more specific information as to the basis for the selection of cases. Murphy<sup>62</sup> has described a small series of patients in whom particular attention was given to involvement of the joints and to the presence of nodules while they were being given massive doses of salicylates. This author was not impressed with the therapeutic value of such a regimen in ameliorating the involvement of the joints. Further dissenting reports come from Wégria and Smull,<sup>63</sup> of the Presbyterian Hospital in New York, who concluded

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58. Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: II. Effectiveness of Extensive Salicylate Therapy in Cases of Acute Infection, *Arch. Int. Med.* **78**:170 (Aug.) 1946.

59. Griffith, G. C.: Rheumatic Fever: Its Recognition and Treatment, *J.A.M.A.* **133**:974 (April 5) 1947.

60. Taran, L. M.: Treatment of Acute Rheumatic Fever and Acute Rheumatic Heart Disease, *Am. J. Med.* **2**:285, 1947.

61. Warren, H. A.; Higley, C. S., and Coombs, F. S.: The Effect of Salicylates on Acute Rheumatic Fever, *Am. Heart J.* **32**:311, 1946.

62. Murphy, G. E.: Salicylate and Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **77**:1, 1945.

63. Wégria, R., and Smull, K.: Salicylate Therapy in Acute Rheumatic Fever, *J. A. M. A.* **129**:485 (Oct. 13) 1945.

that large doses of the drug did not shorten the rheumatic attack, and from Harris,<sup>64</sup> who decided that it was doubtful that massive doses of salicylates suppressed the inflammatory reaction of rheumatic fever. Smull and her associates<sup>65</sup> have reported that when sodium salicylate and sodium bicarbonate are given in equal amounts the latter drug produces an appreciable depression of the salicylate blood level. On the other hand, Griffith<sup>66</sup> believes that smaller doses of bicarbonate do not have this effect yet counteract the tendency to gastric irritation.

The prothrombinopenic effects of massive salicylate therapy have been investigated by Owen and Bradford,<sup>66</sup> who employed 10 Gm. doses of sodium salicylate intravenously daily for six days or longer and found a depression of the prothrombin blood level of as much as 50 per cent. No serious hemorrhages occurred in their series of 25 patients, however, and they observed a tendency to a spontaneous return to normal blood levels despite continued therapy. A slight to moderate increase in the prothrombin time has also been reported by Butt and his associates.<sup>67</sup> Shapiro<sup>68</sup> has found that synthetic vitamin K is effective in counteracting this thrombinopenic action of salicylates. Two deaths, possibly attributable to intravenous and oral salicylate therapy respectively, have been described by Ashworth and McKemie.<sup>69</sup> Postmortem examination of both patients revealed diffuse petechial hemorrhages throughout the body, including the brain; however, in neither case were salicylate or prothrombin levels reported.

A new drug, the calcium double salt of benzoic acid and succinic acid benzyl ester, has been used by Gubner and Szucs<sup>70</sup> in 55 patients

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64. Harris, T. N.: The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever, *Am. J. M. Sc.* **213**:482, 1947.

65. Smull, K.; Wégria, R., and Leland, J.: The Effect of Sodium Bicarbonate on the Serum Salicylate Level During Salicylate Therapy of Patients with Acute Rheumatic Fever, *J.A.M.A.* **125**:1173 (Aug. 26) 1944.

66. Owen, G. C., and Bradford, H. A.: The Prothrombinopenic Effect of Massive Salicylate Therapy in Acute Rheumatic Fever, *Ann. Int. Med.* **25**:97, 1946.

67. Butt, H. R.; Leake, W. H.; Solley, R. F.; Griffith, G. C.; Huntington, R. W., and Montgomery, H.: Studies in Rheumatic Fever: Physiologic Effect of Sodium Salicylate on Human Being, with Particular Reference to Prothrombin Level of Blood and Effect on Hepatic Parenchyma, *J.A.M.A.* **128**:1195 (Aug. 25) 1945.

68. Shapiro, S.: Studies on Prothrombin: VI. The Effect of Synthetic Vitamin K on the Prothrombinopenia Induced by Salicylate in Man, *J.A.M.A.* **125**:546 (June 24) 1944.

69. Ashworth, C. T., and McKemie, J. F.: Hemorrhagic Complications with Death Probably from Salicylate Therapy: Report of Two Cases, *J.A.M.A.* **126**:806 (Nov. 25) 1944.

70. Gubner, R.; and Szucs, M.: Therapeutic Measures in Rheumatic Fever, *New England J. Med.* **233**:652, 1945.

with active rheumatic infection. They have reported a shorter period of hospitalization, less fever and leukocytosis, a shorter period of elevation of the sedimentation rate and a lower incidence of carditis than when patients with apparently similar characteristics were treated with salicylates and ascorbic acid. These writers theorized that the drug may prevent inactivation of certain enzymes concerned in tissue oxidation. Further confirmation of these results is awaited. The value of a 50 per cent oxygen atmosphere for patients with acute rheumatic fever has been described in England by Poulton<sup>71</sup> and in this country by Taran<sup>60</sup>; the latter has found this adjunct to other therapy to be of great benefit in the presence of heart failure in lessening pyrexia, slowing the pulse rate and combating cardiac insufficiency. It is his belief that cardiac disability is minimized by this measure although the period of rheumatic activity is not shortened.

Favorable accounts of the efficacy of sulfonamide drugs in the prevention of rheumatic recurrences have been given by Thomas,<sup>72</sup> Dodge and her associates,<sup>73</sup> Wolf, Rauh and Lyon<sup>74</sup> and others. Thomas has stated: "Small daily doses of sulfonamides . . . seem to be the most effective method of preventing recrudescences that has yet been found," and she recommends that sulfadiazine be given to all children and young adults who have had one or more unequivocal attacks of rheumatic fever. During the early years of World War II it was the experience of medical officers in both the army (Holbrook<sup>75</sup>) and navy (Coburn<sup>76</sup>) that streptococcic epidemics could be checked by the use of sulfadiazine. Such programs, as a recent editorial<sup>77</sup> has pointed out, have certain drawbacks which are not always apparent at first glance. These unfavorable factors include sensitization of persons to the drugs, occasional toxic effects, failure to eliminate throat cultures which yield streptococci and the development of strains of hemolytic streptococci which are resistant to the sulfonamide compounds.

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71. Poulton, cited by Taran.<sup>60</sup>

72. Thomas, C. B.: The Prevention of Recurrences in Rheumatic Subjects, *J.A.M.A.* **126**:490 (Oct. 21) 1944.

73. Dodge, K. G.; Baldwin, J. S., and Weber, M. W.: The Prophylactic Use of Sulfanilamide in Children with Active Rheumatic Fever, *J. Pediat.* **24**:483, 1944.

74. Wolf, R. E.; Rauh, L. W., and Lyon, R. A.: The Prevention of Rheumatic Recurrences in Children by the Use of Sulfathiazole and Sulfadiazine, *J. Pediat.* **28**:516, 1945.

75. Holbrook, W. P.: The Army Air Forces' Rheumatic Fever Control Program, *J.A.M.A.* **126**:84 (Sept. 9) 1944.

76. Coburn, A. F.: The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in United States Navy, *J.A.M.A.* **126**:88 (Sept. 9) 1944.

77. Dangers of Chemoprophylaxis, editorial, *New England J. Med.* **234**: 487, 1946.

All these objections have been sustained by clinical experience and must receive due consideration whenever the question of chemoprophylaxis arises.

#### BACTERIAL ENDOCARDITIS

It has customarily been thought that the alpha hemolytic streptococcus was the offending organism in approximately 90 per cent of the cases of subacute bacterial endocarditis, and it has been the practice of most laboratories to label a streptococcus which produced alpha hemolysis with that descriptive designation. Wheeler and Foley<sup>78</sup> obtained streptococci from 21 patients with subacute bacterial endocarditis and by suitable cultural methods ascertained that seventeen of these belonged to Lancefield group D (commonly considered the enterococcus group): They believed that this was the correct classification, even though the reaction of these bacterial strains on 5 per cent horse blood agar was in most instances that of alpha or beta hemolysis, and they refer to Lancefield's statement that hemolytic activity is not so closely related to serologic grouping as was first supposed. In the light of this work it may be well to carry out more detailed cultural study on all streptococci isolated in cases of endocarditis. Loewe and his associates<sup>79</sup> have recently reported isolation of a strain of nonhemolytic streptococci in 41 cases of subacute bacterial endocarditis. They have named this strain *Streptococcus s.b.e.* and believe that it is unusually resistant to penicillin. There are many instances recorded in the literature of streptococci acquiring an increasing resistance to penicillin; Dowling, Hirsh and O'Neil<sup>80</sup> have reported a case of endocarditis in which the offending *Streptococcus viridans* increased its resistance to penicillin more than a hundredfold during the course of treatment.

Interesting observations have been made by Beeson, Brannon and Warren<sup>81</sup> on the sites of removal of bacteria from the blood stream in 6 patients with bacterial endocarditis. These workers obtained blood from the femoral artery, femoral, hepatic, renal and antecubital veins.

78. Wheeler, S. M., and Foley, G. E.: A Note on the Serologic Classification of Streptococci Isolated from Subacute Bacterial Endocarditis, *Am. Heart J.* **30**:511, 1945.

79. Loewe, L., and Altire-Werber, E.: Clinical Manifestations of Subacute Bacterial Endocarditis Caused by *Streptococcus s.b.e.*; *Am. J. Med.* **1**:353, 1946. Loewe, L.; Plummer, N.; Niven, C. F., Jr., and Sherman, J. M.: *Streptococcus s.b.e.* in Subacute Bacterial Endocarditis, *J.A.M.A.* **130**:257 (Feb. 2) 1946.

80. Dowling, H. F.; Hirsh, H. L., and O'Neil, C. B.: Studies on Bacteria Developing Resistance to Penicillin Fractions X and G in Vitro and in Patients Under Treatment for Bacterial Endocarditis, *J. Clin. Investigation* **25**:665, 1946.

81. Beeson, P. B.; Brannon, E. S., and Warren, J. V.: Observations on the Sites of Removal of Bacteria from the Blood in Patients with Bacterial Endocarditis, *J. Exper. Med.* **81**:9, 1945.



superior vena cava and right auricle. The arterial and venous specimens were taken at approximately the same moment and cultured, and the number of colonies per cubic centimeter were then counted. Their results disclosed that the arterial blood had a colony count higher, as a rule, than that of blood from the right auricle, indicating that a new supply of bacteria was constantly being added from the vegetations. Their studies also showed a remarkable constancy of the arterial colony count from minute to minute and not a series of showers of bacteria. The smallest number of colonies appeared in cultures of blood drawn from the hepatic vein (as low as 5 per cent of the arterial count); hence it was surmised that the liver acted as an effective bacterial filter. These authors also concluded that the degree of bacteremia present in arterial blood and in blood from the antecubital vein was so nearly the same that there was no reason to perform arterial cultures routinely. Investigations of a somewhat similar nature have been conducted by Mallén, Hube and Brenes,<sup>82</sup> who obtained cultures of blood from the sternal marrow, radial artery and antecubital vein in 88 patients with subacute bacterial endocarditis. Their results do not indicate that any one of these sites is definitely superior to the others in yielding positive blood cultures.

The treatment of 8 patients with acute bacterial endocarditis has been made the subject of a report by Wilhelm, Hirsh, Hussey and Dowling.<sup>83</sup> Five of these patients are said to have been infected with the *Staphylococcus albus*, 2 with the *Staphylococcus aureus*, and 1 with type XII pneumococcus. All of them received penicillin, but only 3 survived. Unusual features in this series were the apparent involvement of the tricuspid valve in 4 cases (confirmed at autopsy in 1) and the fact that 5 out of the 8 were addicted to heroin. The diagnosis of acute bacterial endocarditis is indeed difficult at any age, and Zeman and Siegal,<sup>84</sup> in describing 9 patients, 60 or more years of age, who showed this disease at autopsy, point out that in no instance was the correct diagnosis made clinically. In at least 2 of the patients no murmurs were heard.

The introduction of antibiotics in the treatment of subacute bacterial endocarditis has brought forth numerous publications describing various methods of administration; dosages, concomitant use of other drugs

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82. Mallén, M. S.; Hube, E. L., and Brenes, M.: Comparative Studies of Blood Cultures Made from Artery, Vein, and Bone Marrow in Patients with Subacute Bacterial Endocarditis, *Am. Heart J.* **33**:692, 1947.

83. Wilhelm, F.; Hirsh, H. L.; Hussey, H. H., and Dowling, H. F.: The Treatment of Acute Bacterial Endocarditis with Penicillin, *Ann. Int. Med.* **26**: 221, 1947.

84. Zeman, F. D., and Siegal, S.: Acute Bacterial Endocarditis in the Aged. *Am. Heart J.* **29**:597, 1945.

and clinical results. To Loewe and his associates<sup>85</sup> must go great credit for persevering in the treatment of this disease and finally demonstrating the value of large doses of penicillin. Their original report included data on 7 patients, in all of whom penicillin-sensitive organisms were demonstrated and all of whom showed excellent clinical responses to what we now consider modest doses of the drug. In this and in his subsequent papers Loewe has preached the wisdom of using combined penicillin and heparin treatment to retard the formation of vegetations and to hasten their disappearance. Of 54 patients whom he treated in this manner, 37 were living after a period of observation of two to fifteen months. He advises a five week course of penicillin and heparin, the former to be given in a daily dose of at least 200,000 units by the intravenous route. From his reports it does not appear that the administration of heparin has been a significant factor in any of the deaths in his series. Thill and Meyer<sup>86</sup> gave penicillin with "dicumarol" in the treatment of 13 patients with subacute bacterial endocarditis and also administered penicillin alone to another group of 9 patients. Eleven of the patients receiving the combined therapy were considered to have recovered or to have had their disease "arrested," whereas only 3 patients in the group receiving penicillin alone were alive at the time of the report. It does not appear, however, that the two groups of cases were strictly comparable; indeed the authors are themselves skeptical about the value of anticoagulant therapy in this condition. It is fair to state that no definite conclusion can be drawn from their experience.

It is the opinion of most writers on this subject that anticoagulants are unnecessary to obtain satisfactory clinical results from the penicillin therapy of bacterial endocarditis. This view appears to be well substantiated by the reports referred to subsequently in which penicillin alone has been administered in cases of endocarditis. Perhaps of an importance equal to or greater than this clinical demonstration of the efficacy of penicillin given alone is the experimental work of Nathanson and Liebhold.<sup>87</sup> These authors prepared fibrin pour plates to which a stock culture of *Bacillus subtilis* had been added and then determined the diffusion of penicillin, sodium sulfathiazole and sodium sulfadiazine

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85. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis: Report of Seven Consecutive Successfully Treated Patients, *J.A.M.A.* **124**:144 (Jan. 15) 1944. Loewe, L.: The Combined Use of Anti-Infectives and Anti-Coagulants in the Treatment of Subacute Bacterial Endocarditis, *Bull. New York Acad. Med.* **21**: 59, 1945.

86. Thill, C. J., and Meyer, O. O.: Experiences with Penicillin and Dicumarol in the Treatment of Subacute Bacterial Endocarditis, *Am. J. M. Sc.* **213**:300, 1947.

87. Nathanson, M. H., and Liebhold, R. A.: Diffusion of Sulfonamides and Penicillin into Fibrin, *Proc. Soc. Exper. Biol. & Med.* **62**:83, 1946.

into the medium, using the assay cup technic. Their results indicated that penicillin penetrated almost as well into fibrin pour plates as into plain agar plates, in contrast to an insignificant degree of penetration into the former by the sulfonamide compounds. This work provides a rational basis for the belief that penicillin given alone can be successful in reaching bacteria lodged in fibrinous vegetations without resort to anticoagulants.

The numerous reports on the treatment of subacute bacterial endocarditis with penicillin but without anticoagulants give the over-all survival rate as about 65 per cent. Goerner, Geiger and Blake<sup>88</sup> described 12 patients treated with moderate doses of the drug given by constant intravenous infusion, 11 of whom were surviving at the time of the report. Flippen and his associates<sup>89</sup> have studied 20 patients, 12 of whom have survived. The Medical Research Council in Great Britain<sup>90</sup> has stated that of 147 patients treated by means of the constant intravenous drip or by intermittent intramuscular injections 81 were apparently cured over a minimum follow-up period of three months. The statistics reported from the Presbyterian Hospital in New York by Hunter<sup>91</sup> indicate that 41 patients of 49 who have been treated with the drug are alive and well, and Priest and his colleagues<sup>92</sup> found a survival rate of 65 per cent in 34 of their cases. It does not appear from these and other publications that the route of administration of penicillin is the vital factor in the production of successful results.

In this regard Loewe and his group<sup>93</sup> have found that the continuous intravenous drip provides higher serum levels of penicillin than does the continuous intramuscular route or fractional intramuscular injections when a comparable daily dosage is used, and Rantz and Kirby,<sup>94</sup>

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88. Goerner, J. R.; Geiger, A. J., and Blake, F. G.: Treatment of Subacute Bacterial Endocarditis with Penicillin: Report of Cases Treated Without Anticoagulant Agents, *Ann. Int. Med.* **23**:491, 1945.

89. Flippen, H. F.; Mayock, R. L.; Murphy, F. D., and Wolferth, C. C.: Penicillin in the Treatment of Subacute Bacterial Endocarditis: Preliminary Report on Twenty Cases Treated over One Year Ago, *J.A.M.A.* **129**:841 (Nov. 24) 1945.

90. Success in Bacterial Endocarditis, Annotations, *Lancet* **1**:390, 1946.

91. Hunter, T. H.: Treatment of Subacute Bacterial Endocarditis, *Mod. Conc. Cardiovasc. Dis.*, 1946, vol. 15, no. 8.

92. Priest, W. S.; Smith, J. M., and McGee, C. J.: Penicillin Therapy of Subacute Bacterial Endocarditis, *Arch. Int. Med.* **79**:333 (March) 1947.

93. Loewe, L.; Rosenblatt, P.; Russell, M., and Altire-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual Serum Levels of Penicillin: Comparative Studies with Particular Reference to Fractional and Continuous Intramuscular Administration, *J. Lab. & Clin. Med.* **30**:730, 1945.

94. Rantz, L. A., and Kirby, W. M. M.: The Absorption of Penicillin Following Continuous Intravenous and Subcutaneous Administration, *J. Clin. Investigation* **23**:789, 1944.

investigating the blood level obtained with constant subcutaneous administration as compared with that obtained by the constant intravenous method, have reported that the latter gives levels which are 50 per cent higher. It is apparent from the reports available, however, that the route of administration is not as important as are the daily dose of the drug, the duration of treatment, the sensitivity of the organism to penicillin and the height of the penicillin blood levels. Most writers on the subject now advise a minimal daily dose of 500,000 units given in an uninterrupted course for four weeks or longer. A blood level of penicillin five times that necessary to inhibit growth of the organism *in vitro* is desirable.

Mention must also be made of the use of streptomycin in the occasional case of endocarditis in which a gram-negative organism is cultured from the blood stream or in which some other type of bacteria is being harbored which is found to be extremely resistant to penicillin but sensitive to streptomycin. Hunter and Duane<sup>95</sup> have described 1 patient who was infected with a small gram-negative bacillus (unidentified) and who responded well to a ten day course of streptomycin in doses of 3.0 Gm. daily. The successful use of this drug in the treatment of 2 patients with streptococcic bacterial endocarditis has also been reported by Priest and McGee<sup>96</sup> (although there is some doubt with regard to 1 of these patients as to whether penicillin or streptomycin or both should be credited with the good result):

The outlook for patients with bacterial endocarditis has thus changed dramatically for the better during the past three years. Nevertheless there continue to be numerous deaths from the ravages of this disease despite the control of the bacterial infection itself. As White, Mathews and Evans,<sup>97</sup> Rosenblatt and Loewe,<sup>98</sup> Fiese,<sup>99</sup> and Honigman and Karns<sup>100</sup> have reported, there is an appreciable number of patients who succumb to congestive heart failure because of the destructive

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95. Hunter, T. H., and Duane, R. B., Jr.: Subacute Bacterial Endocarditis Due to Gram-Negative Organisms, *J.A.M.A.* **132**:209 (Sept. 28) 1946.

96. Priest, W. S., and McGee, C. J.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis: Report of Three Cases, *J.A.M.A.* **132**:124 (Sept. 21) 1946.

97. White, P. D.; Mathews, M. W., and Evans, E.: Notes on the Treatment of Subacute Bacterial Endocarditis Encountered in Eighty-Eight Cases at the Massachusetts General Hospital During the Six Year Period 1939 to 1944 (Inclusive), *Ann. Int. Med.* **22**:61, 1945.

98. Rosenblatt, P., and Loewe, L.: Healed Subacute Bacterial Endocarditis, *Arch. Int. Med.* **76**:1 (July) 1945.

99. Fiese, M. J.: Cardiac Failure in Penicillin-Treated Subacute Bacterial Endocarditis, *Arch. Int. Med.* **79**:436 (April) 1947.

100. Honigman, A. H., and Karns, J. R.: Healed Subacute Bacterial Endocarditis: Report of Two Cases with Death Due to Congestive Heart Failure, *Ann. Int. Med.* **26**:704, 1947.

effect of ulceration of the heart valves and endocardial surfaces (as well as the concomitant presence of rheumatic activity) and who at autopsy show proof of a sterilization and healing of the cardiac lesions. To this group should be added those whose deaths are attributable to embolic phenomena occurring during the course of treatment.

#### HYPERTENSION AND HYPERTENSIVE HEART DISEASE

The range of the blood pressure in hypertensive persons has been studied by Gubner, Silverstone and Ungerleider,<sup>101</sup> who found that the maximum blood pressure levels obtained by breath-holding tests and cold pressor tests were approximately similar. These authors also state that hyperventilation accompanied with digital pressure over one carotid sinus (preferably the left one) gave a fall in blood pressure comparable to that obtained by sedation with "sodium amytal." These simple diagnostic measures deserve further trial to ascertain their clinical value. Roth and his colleagues<sup>102</sup> from the Mayo Clinic have subjected a number of normal subjects to various studies before and after they smoked two cigarets in succession. In addition to a drop in skin temperature and the appearance of tachycardia, an elevation in blood pressure of a significant degree was produced, the systolic level rising an average of 19 mm. of mercury and the diastolic level rising an average of 14 mm. These authors draw no conclusions as to the undesirability of tobacco for hypertensive persons. An extensive study of the records of 22,741 army officers has been carried out by Levy, White, Stroud and Hillman,<sup>103</sup> and their findings are of considerable interest to all physicians who have the problem of predicting physical fitness and the individual life span, particularly in connection with the armed forces and in the insurance field. It was noted that at all ages sustained hypertension developed more frequently in those with previous

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101. Gubner, R.; Silverstone, F., and Ungerleider, H. E.: Range of Blood Pressure in Hypertension, *J.A.M.A.* **130**:325 (Feb. 9) 1946.

102. Roth, G. M.; McDonald, J. B., and Sheard, C.: The Effect of Smoking Cigaretts and of Intravenous Administration of Nicotine on Electrocardiogram, Basal Metabolic Rate, Cutaneous Temperature, Blood Pressure and Pulse Rate of Normal Persons, *J.A.M.A.* **125**:761 (July 15) 1944.

103. Levy, R. L.; Hillman, C. C.; Stroud, W. D., and White, P. D.: Transient Hypertension: Its Significance in Terms of Later Development of Sustained Hypertension and Cardiovascular-Renal Diseases, *J.A.M.A.* **126**:829 (Nov. 25) 1944. Levy, R. L.; White, P. D.; Stroud, W. D., and Hillman, C. C.: Transient Hypertension: The Relative Prognostic Importance of Various Systolic and Diastolic Levels, *J.A.M.A.* **128**:1059 (Aug. 11) 1945; Transient Tachycardia: Prognostic Significance Alone and in Association with Transient Hypertension, *J.A.M.A.* **129**:585 (Oct. 27) 1945; Overweight: Its Prognostic Significance in Relation to Hypertension and Cardiovascular-Renal Diseases, *J.A.M.A.* **131**:951 (July 20) 1946.

transient hypertension than in those who never showed an elevation of blood pressure. It was found, too, that even a slight degree of elevation in the blood pressure level was of importance and that a transient rise in diastolic pressure above 100 mm. of mercury was of great significance. The presence of overweight or of transient tachycardia and in particular the combination of these two also increased the incidence of later sustained hypertension.

That commonly mentioned condition, menopausal hypertension, has been critically studied by Taylor and his associates,<sup>104</sup> whose subjects were 179 castrated women and a group of 21 women who had undergone the natural menopause. They concluded that there was no increase in the incidence of hypertension which could be attributed to the onset of the menopause.

An excellent study of the differential diagnosis of terminal glomerulonephritis and malignant hypertension has been reported by the same authors.<sup>105</sup> With regard to renal status, they conclude that there was less effective renal blood flow, plasma "diodrast" clearance and plasma inulin clearance, a lower filtration fraction, a lower serum level of protein and albumin and a lower mean of systolic and diastolic pressure on the average in patients with nephritis than in patients suffering from malignant hypertension. It was also observed that once renal failure commenced the nephritic patients survived longer than did those with malignant hypertension. They postulate that hypoproteinemia may serve as a mechanism by which glomerular filtration is maintained. Regarding the cardiac status, they conclude that heart failure tends to develop earlier and more frequently in patients with malignant hypertension than in those with primary renal disease and that electrocardiographic abnormalities were commoner in the former group.

The effect of desoxycorticosterone acetate on the blood pressure of man has been investigated by Perera, Knowlton, Lowell and Loeb.<sup>106</sup> They administered the drug daily or every other day by the subcutaneous route to 24 patients with Addison's disease and found that 8 of these were persistently hypertensive while under treatment. Salt therapy alone in 15 patients did not appear to alter the blood pressure level. Hypertension also developed in 3 normal persons while they were

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104. Taylor, R. D.; Corcoran, A. C., and Page, I. H.: Menopausal Hypertension: A Critical Study, *Am. J. M. Sc.* **213**:475, 1947.

105. Corcoran, A. C., and Page, I. H.: Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension: I. Renal Aspects, *Ann. Int. Med.* **21**:747, 1944. Taylor, R. D.; Kohlstaedt, K. G.; Richter, A. B., and Page, I. H.: Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension: II. Cardiac Aspects, *Ann. Int. Med.* **21**:765, 1944.

106. Perera, G. A.; Knowlton, A. I.; Lowell, A., and Loeb, R. F.: Effect of Desoxycorticosterone Acetate on the Blood Pressure of Man, *J.A.M.A.* **125**:1030 (Aug. 12) 1944.

receiving desoxycorticosterone acetate, but their blood pressure returned to normal when the medication was stopped. Their studies appeared to eliminate abnormal retention of sodium ion or an increase in circulating blood volume as the significant factor producing the elevation in blood pressure.

Goldblatt<sup>107</sup> has published a comprehensive review of the evidence for the renal origin of hypertension. He commences by remarking: "There is no reasonable doubt that some cases of human hypertension are of renal origin. The unsolved problem is whether many or most of those still referred to as 'essential' are also of renal origin." It is his belief that "arterial and arteriolar sclerosis are primary but of unknown origin, and when vascular disease affects the kidneys to a degree sufficient to produce adequate disturbance of intrarenal hemodynamics, a mechanism is initiated which brings about the increased peripheral vascular resistance that determines the hypertension." He summarizes his own study of the production of an elevation of the blood pressure in animals and reviews the evidence for the humoral mechanisms in hypertension. In conclusion he discusses the similarities between human essential and experimental renal hypertension and reasons that in view of these it would be remarkable if the former would not prove to be of renal origin.

The treatment of arterial hypertension by the several technics of sympathectomy has its advocates and its opponents. On the one hand, Smithwick<sup>108</sup> and de Takats and others<sup>109</sup> believe that the operation is the procedure of choice in "selected" cases of this disease. On the other hand, Kerr<sup>110</sup> voices a skeptical attitude when he remarks that sympathectomy may be "another example of the mastery of technique over reason." It is clear from the literature that the tests which are employed in the selection of patients for sympathectomy are far from ideal in yielding prognostic information. It should also be pointed out that there is no series available in which truly comparable groups of patients have been treated alternately by the same workers with some type of medical regimen and by sympathectomy. It is the opinion

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107. Goldblatt, H.: The Renal Origin of Hypertension, *Physiol. Rev.* **27**: 120, 1947.

108. (a) Smithwick, R. H.: Surgical Treatment of Hypertension: Effect of Radical (Lumbodorsal) Splanchnicectomy on Hypertensive State of One Hundred and Fifty-six Patients Followed One to Five Years, *Arch. Surg.* **49**:180 (Sept.) 1944; (b) Medical Progress: Surgery of the Autonomic Nervous System, *New England J. Med.* **236**:662, 1947.

109. de Takats, G.; Graupner, G. W.; Fowler, E. F., and Jensik, R. J.: Surgical Approach to Hypertension: Second Report, *Arch. Surg.* **53**:111 (Aug.) 1946.

110. Kerr, W. J.: Therapeutic "Information Please": Cardiovascular Disease, *J.A.M.A.* **132**:972 (Dec. 21) 1946.

of Palmer<sup>111</sup> that the longer patients are followed after operation the less favorable the results appear, although he agrees that sympathectomy is the treatment of choice in most cases of malignant hypertension. In his paper he also cites and discusses the multiple disadvantages attending the procedure and the convalescence therefrom. Smithwick<sup>108a</sup> reports a series of 156 patients on whom he has operated; 61 per cent of these showed significant lowering of the blood pressure one to five years later associated with symptomatic relief and objective improvement in the status of the eyes, heart and kidneys. More recently, Peet<sup>112</sup> has reported symptomatic improvement among 86 per cent of his surviving patients, as well as a significant reduction in the blood pressure in 81 per cent. De Takats,<sup>109</sup> Hammarström<sup>113</sup> and Poppen<sup>114</sup> also have published statistics indicating a 50 per cent or greater symptomatic and objective improvement in suitable cases. The operative mortality has not been greater than 2 per cent. Rojas, Smithwick and White<sup>115</sup> have published statistics to refute the concept that the reduction in blood pressure following sympathectomy is a nonspecific effect related to a major operative procedure and convalescence therefrom.

It has been the experience of Grimson<sup>116</sup> that the sedation test with "sodium amytal" has not been of great prognostic value for his patients who underwent sympathectomy for hypertension. The use of tetraethyl ammonium compounds in hypertension, both as a possible therapeutic agent and in a preoperative test, has been investigated by Lyons and his group<sup>117</sup> at the University of Michigan Medical School. They report on the pharmacologic properties of this new group of drugs which appear to block the transmission of nerve impulses through autonomic ganglions and which have, among other actions, the effect of producing moderate to profound transient hypotension. Most, but not all, hypertensive patients when administered one of these drugs intravenously exhibit a decided drop in blood pressure associated in certain

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111. Palmer, R. S.: A Medical Evaluation of the Surgical Treatment of Hypertension, *J.A.M.A.* **134**:9 (May 3) 1947.

112. Peet, M. M.: Results of Bilateral Supradiaphragmatic Splanchnicectomy for Arterial Hypertension, *New England J. Med.* **236**:270, 1947.

113. Hammarström, S.: Arterial Hypertension: I. Variability of Blood Pressure; II. Neurosurgical Treatment, *Acta Med. Scandinav.*, 1947, supp. 192, p. 20.

114. Poppen, J. L., and Lemmon, C.: The Surgical Treatment of Essential Hypertension, *J.A.M.A.* **134**:1 (May 3) 1947.

115. Rojas, F.; Smithwick, R. H., and White, P. D.: Nonspecific Major Operations and Lumbodorsal Sympathectomy: Comparison Between Their Effects on Blood Pressure, *J.A.M.A.* **126**:15 (Sept. 2) 1944.

116. Grimson, K. S.; Kernodle, C. E., and Hill, H. C.: Hypertension, *J.A.M.A.* **126**:218 (Sept. 23) 1944.

117. Lyons, R. H.; Moe, G. K.; Neligh, R. B.; Hoobler, S. W.; Campbell, K. N.; Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man with Tetraethylammonium, *Am J. M. Sc.* **213**:315, 1947.



instances with a relief of headache and other symptoms. Birchall and others<sup>118</sup> employed tetraethyl ammonium chloride preoperatively in 12 hypertensive patients and were disappointed during a short period of follow-up by the lack of correlation between the hypotensive effects obtained preoperatively with this drug and the apparent fall in blood pressure resulting from sympathectomy (using the Smithwick technic).

Methods of treatment of arterial hypertension other than sympathectomy have attracted considerable attention during the past few years, notably those employing special diets. Of great interest has been the work of Kempner,<sup>119</sup> at Duke University, who has employed a diet of rice, fruit and sugar in patients with both essential hypertension and primary renal disease. It is his belief that the ordinary mixed diet may contain constituents which increase the production of "abnormal" harmful substance by diseased renal cells. In the hope of compensating for renal dysfunction, he has administered a 2,000 calory diet limited to rice, sugar, fruit and fruit juices and supplemented by vitamins and iron. This regimen, which is hardly designed to delight the stomach of the gourmet, allows a daily intake of approximately 460 Gm. of carbohydrate, 20 Gm. of protein and 5 Gm. of fat. The fluid intake he has limited to 1,000 cc. of fruit juice daily. Of a group of 129 patients suffering from essential hypertension, 65 showed subjective and objective improvement; in many of these the blood pressure returned to normal. He has similarly noted benefit from the diet in cases of primary renal disease. In certain cases when the maximum of improvement seems to have been attained a liberalization of the type of food to be ingested has been allowed. Good results from the use in hypertension of a low sodium diet alone have also been reported by Bryant and Blecha<sup>120</sup> and by Grollman and his associates.<sup>121</sup> These investigations hold considerable promise for the future, not only in offering an inexpensive and painless type of therapy but also in providing a form of treatment which may be offered to patients for whom sympathectomy is obviously not suitable. Kempner<sup>119a</sup> has suggested that perhaps impaired renal metabolism is the

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118. Birchall, R.; Taylor, R. D.; Lowenstein, B. E., and Page, I. H.: Clinical Studies of the Pharmacologic Effects of Tetraethyl Ammonium Chloride in Hypertensive Persons Made in an Attempt to Select Patients Suitable for Lumbodorsal Sympathectomy and Ganglionectomy, *Am. J. M. Sc.* **213**:572, 1947.

119. Kempner, W.: (a) Compensation of Renal Metabolic Dysfunction, *North Carolina M. J.* **6**:61, 1945; (b) Some Effects of the Rice Diet in the Treatment of Kidney Disease and Hypertension, *Bull. New York Acad. Med.* **22**:358, 1946.

120. Bryant, J. M., and Blecha, E.: Low Sodium—Forced Fluid Management of Hypertensive Vascular Disease and Hypertensive Heart Disease, *Proc. Soc. Exper. Biol. & Med.* **65**:227, 1947.

121. Grollman, A.; Harrison, T. R.; Mason, M. F.; Baxter, J.; Crampton, J., and Reichsman, F.: Sodium Restriction in the Diet for Hypertension, *J.A.M.A.* **129**:533 (Oct. 20) 1945.

chief difficulty when the rice diet is successful and that patients who show no response to his regimen may have hypertension due to an extrarenal factor. Such a postulate remains to be investigated further, and indeed the whole mechanism of the rice diet or the low sodium diet (the former includes the latter, of course) requires more study.

Another approach to this problem is that of Pendergrass and his colleagues<sup>122</sup> at the University of Pennsylvania, who have for some time been using roentgen therapy of the pituitary gland in patients with arterial hypertension, selecting their cases on the basis of the presence of antidiuretic hormone in the blood serum. These authors assume that the presence of this hormone is an indication of increased pituitary activity and that an excess of the pituitary pressor hormone may also exist. Of 93 such patients whom they have treated and on whom adequate follow-up data are available, approximately one half are said to have shown improvement in their clinical condition and blood pressure levels. That this form of treatment is not without its dangers is obvious from the fact that coma and convulsive seizures developed in 3 patients after radiation of the pituitary region. A more complete clinical report of the cases, with the addition of a control series, would be desirable.

Binger,<sup>123</sup> in a preliminary report on a group of 24 hypertensive patients studied from the point of view of personality disorders, observed certain common psychologic traits which may distinguish sufferers from this disease. He writes: "It is . . . my suspicion that the psychological disorder and the physiological disorder each represents a different aspect of a more basic disturbance, the nature and cause of which is unknown." He concludes that there is no psychotherapeutic procedure available which can change the course of the disease but reminds us that "almost all our therapy is in essence psychotherapy."

Many recent reports of hypertension<sup>124</sup> due to the presence of a pheochromocytoma have appeared during the past three and a half

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122. Pendergrass, E. P.; Griffith, J. O., Jr.; Padis, N., and Barden, R. P.: The Indications for Irradiation of the Pituitary Gland in Patients with Arterial Hypertension, *Am. J. M. Sc.* **213**:192, 1947.

123. Binger, C.: A Critique of Psychotherapy in Arterial Hypertension, *Bull. New York Acad. Med.* **21**:610, 1945.

124. Thorn, G. W.; Hindle, J. A., and Sandmeyer, J. A.: Pheochromocytoma of the Adrenal Associated with Persistent Hypertension: Case Report, *Ann. Int. Med.* **21**:122, 1944. Green, D. M.: Pheochromocytoma and Chronic Hypertension, *J.A.M.A.* **131**:1260 (Aug. 17) 1946. Pheochromocytoma; Left Adrenal Gland, Massachusetts General Hospital Case 32511, *New England J. Med.* **235**:906, 1946. Muntz, H. H.; Ritchey, J. O., and Gatch, W. D.: Adrenalin Producing Tumor (Pheochromocytoma) Containing 2,300 mg. of Adrenalin, *Ann. Int. Med.* **26**: 133, 1947. Snyder, C. H., and Vick, E. H.: Hypertension in Children Caused by Pheochromocytoma: Report of Three Cases and a Review of Literature, *Am. J. Dis. Child.* **73**:581 (May) 1947.

years. It is worth while to mention once again the fact, which is obvious from these case histories, that this type of tumor does not necessarily produce a paroxysmal type of hypertension and that a persistent elevation of the blood pressure is not uncommonly observed. A moderate to considerable elevation of the basal metabolic rate may be found in certain cases. The histamine test for the diagnosis of this condition has been introduced by Roth and Kvale,<sup>125</sup> and while such a procedure may be of considerable value in diagnosis, further experience with it is necessary to estimate its reliability and hazards. Rather alarming reactions may occur with its use, and it is probably a fair conclusion that it should not be employed unless there is considerable doubt of the diagnosis.

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125. Roth, G. M., and Kvale, W. F.: A Tentative Test for Pheochromocytoma, *Am. J. M. Sc.* **210**:653, 1945; A Tentative Test for the Diagnosis of Pheochromocytoma, *J. Lab. & Clin. Med.* **30**:366, 1945.

*(To Be Concluded)*

## Correspondence

### MARFAN'S SYNDROME IN THE ADULT

*Letter to the Editor:*—In the October issue of the ARCHIVES, Tobin, Bay and Humphreys reported 2 interesting cases of Marfan's syndrome in the adult. The patients in both cases died from dissecting aneurysm of the aorta. Although the authors discuss the heredity of this "relatively rare familial symptom complex" in a special paragraph, they come to the conclusion in one of the following paragraphs concerned with "etiologic factor" that Marfan's syndrome is "of unknown origin," and that even twelve available autopsy reports did "not offer any solution as to the cause of the syndrome."

Medical authors, at least those who study and report hereditary familial diseases, should take cognizance of the fact that heredity is an etiologic factor. They also should familiarize themselves with the principles of constitutional pathology, that is, the clinical consequences of human genopathies. The enumeration of the long list of various constitutional abnormalities and malformations frequently encountered with Marfan's syndrome is sufficient proof that this syndrome represents a particular variety of a widespread genopathy known as "status degenerativus." That autopsies fail to elucidate the cause of Marfan's syndrome was clear thirty years ago ("Konstitutionelle Disposition zu inneren Krankheiten," Berlin: Springer, 1917) and has been proved since. It is time to use the bridge between the science of genetics and that of human pathology. The bridge has been built, but only few set foot on it. It is called "constitutional pathology" (see "Constitution and Disease," by J. Bauer, second edition, New York, Grune & Stratton, 1945).

J. BAUER, M.D., Los Angeles.

### MERCURIAL DIURETICS

*To the Editor:*—The opening sentence of Dr. Chapman and Dr. Shaffer in their paper on "Mercurial Diuretics" which appeared in the ARCHIVES (April 1947) is neither in accordance with the facts nor fair to previous workers. They state: "Acute toxicity of mercurial diuretics has been noted frequently, but no extensive investigation of substances to counteract this toxicity has been reported."

This topic sentence, of course, immediately conveys the impression that theirs is the first "extensive investigation" of this nature. To set the record straight, I should like to point out that the work of Pines and his associates (Mercurial Diuretics: The Addition of Magnesium Sulfate to Prevent the Toxic Effects of Their Intravenous Administration, *Brit. Heart J.* 6:197 [Oct.] 1944), cited by Chapman and Shaffer in another regard and published three years before their work, is in my opinion a good deal more extensive than their own investigation and presents a method for reducing mercurial toxicity which is apparently as effective as theirs if not more so.

Incidentally, this work of Pines and others seems to have been overlooked by a number of American cardiologists. DeGraff in a recent symposium at the convention of the American Medical Association stated that he knew of no method to reduce the danger of intravenous administration of mercurial diuretics.

M. J. SMALL, M.D., Parsons, W. Va.

*To the Editor:*—We believe that our investigation of the mercurial diuretics was extensive enough to report the facts. The publication of the investigation by

Pines and his associates did not state the number of animals used, and therefore we could not assume that their investigation was extensive. Their report, however, was complete to that date, and we believe that due recognition was given to this fact.

It is not justifiable to compare our method with theirs as the time interval of injection of a mercurial and a detoxifying substance was considerably different, ours being two and five minutes and theirs thirty minutes. It is reasonable to believe that the longer the time interval of injection the lesser the accumulation of mercury in the circulation to produce a cardiotoxic effect.

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# News and Comment

## GENERAL NEWS

**Death of Dr. William M. Bradshaw, Medical Director of the Mutual Life Insurance Company of New York.**—Funeral services were held on Monday (May 3) at the Central Presbyterian Church, Park Avenue and Sixty-Fourth Street, New York city, for the late Dr. William M. Bradshaw, medical director of the Mutual Life Insurance Company of New York, who died at Roosevelt Hospital in New York on Saturday, May 1. He was 64 years old. Dr. Bradshaw had been with the company since 1917. Prior to that he was adjunct attending physician at Bellevue Hospital. He was graduated from Princeton University in 1905 and from the College of Physicians and Surgeons at Columbia University in 1909. He was a member of the American Medical Association, the New York State Medical Society and the University Club and a fellow of the New York Academy of Medicine.

He is survived by his wife, Mrs. Harriet Haight Bradshaw.

**Grants by the Research Council on Problems of Alcohol.**—A grant of \$20,000 for a study on biochemical and endocrinologic factors in alcoholism was recently made by the Research Council on Problems of Alcohol to the New York University College of Medicine. The study is to be undertaken in the Department of Medicine under the direction of Dr. James J. Smith.

Another grant, of \$30,000, has been made by the Research Council on Problems of Alcohol to Cornell University Medical College for a special investigation in the field of alcoholism.

**Meeting of the International Society of Hematology.**—The biannual meeting of the International Society of Hematology will be held at the Hotel Statler, Buffalo, N. Y., Aug. 23-26, 1948.

The following Symposiums will be presented: general subjects, including radioactive and stable isotopes in hematology; problems and diseases related to the red cells; problems and diseases related to white cells; immunohematology, Rh-Hr (CDE-cde) antigens and antibodies and hemolytic anemias, and coagulation problems and hemorrhagic diseases.

Scientific exhibits will be presented in the south wing of the seventeenth floor of Hotel Statler. Applications for the presentation of scientific exhibits are now being received by Dr. O. P. Jones, Department of Anatomy, University of Buffalo, Buffalo, N. Y. Chairman of the Program Committee is Dr. Ernest Witebsky, Buffalo General Hospital, Buffalo, N. Y.

Dr. Eduardo Uribe Guerola, Leibnitz 212, Nueva Colonia Anzures, México D. F., Mexico, is in charge of the program from South and Central America, and Sir Lionel Whitby, University of Cambridge, Cambridge, England, is in charge of arrangements for the program from Europe. Communications concerning applications for the program will be received by these committeemen.

All scientific sessions and exhibits will be open to scientists interested in hematology. This will, of course, include members of the medical profession and of those branches of science dealing with hematology, such as biochemistry, biophysics, genetics and immunology.

Communications and applications concerning membership will be received by the following members of the membership committee:

- Dr. William Dameshek, Chairman, 25 Bennett St., Boston, for the United States
- Dr. M. Bessis, Laboratoire de Recherches, Du Centre National de Transfusion Sanguine, 53 Boulevard Diderot, Paris, France
- Dr. Robert R. Race, Lister Institute, Chelsea Bridge Road, London S.W. 1, England
- Dr. Ludwik Hirszfeld, Institute of Medical and Microbiological Science, Wroclaw, Poland
- Dr. Ignacio Gonzales Guzman, University of Mexico College of Medicine, México D. F., Mexico
- Dr. Walter Cruz, Instituto Oswaldo Cruz, Caiza Postal 926, Rio de Janeiro, Brazil
- Dr. Alfredo Pavlovsky, Ancherena 1710, Buenos Aires, Argentina
- Dr. Theodore Waugh, McGill University, Montreal, Canada
- Dr. Berger Broman, Royal Caroline Medical School, Stockholm, Sweden
- Dr. C. R. Das Gupta, Hematology Department, Calcutta School of Tropical Medicine, Calcutta, India
- Dr. Luis Sandoval S., Instituto de Histologia de la Universidad de Concepción, Santiago, Chile
- Dr. Rod Sirivejkul, Army Medical Department, Bangkok, Siam
- Dr. Carl Rohr, Medizinischen Universitätsklinik, Zurich, Switzerland
- Dr. Moises Chediak, Laboratorios Chediak, 23 #654 Esq. A., Banos Vedado, Habana, Cuba
- Dr. G. di Guglielmo, Director of Medical Clinics, University of Naples Polyclinic, Naples, Italy
- Dr. Henrik Dam, Danmarks Tekniske Højskole, Biologisk Afdeling, Østervoldgade 10 Trappe L, Copenhagen, Denmark

Those interested in attending the meetings may communicate with Dr. Sol Haberman, Secretary, the William Buchanan Blood Center, Baylor Hospital, Dallas, Texas.

**Memorial Issue in Honor of Sir William Osler.**—The July 1949 number of the ARCHIVES OF INTERNAL MEDICINE will be issued to commemorate the hundredth anniversary of the birth of Sir William Osler. It will contain articles written by many of Dr. Osler's contemporaries and by physicians who worked under him.

If any of the readers of the ARCHIVES have informal pictures of Dr. Osler, it would be appreciated if they would send them to the Editorial Board, 535 North Dearborn Street, Chicago, for possible use in the William Osler number. They will be returned to sender, who will be given due credit for them.

**Appointment of Commissioned Officers in the Medical Corps and Dental Corps of the Regular Navy.**—The statutory authority contained in Public Law 365 of the 80th Congress, Title II (Army-Navy-Public Health Service Medical Officer Procurement Act of 1947), makes it possible now for civilian physicians to become commissioned officers in the regular Navy, provided they meet the professional and physical qualifications. This law is unique in that it does away with, for the first time, the age limitation of 32 years and permits physicians in civilian practice to enter the Navy and be commissioned with the rank up to and including captain. The law considers all strata of the medical profession, i. e., interns, residents, reserves, former medical officers who have resigned and present practicing physicians.

In order to make application, a physician must be a citizen of the United States, a graduate from a class "A" medical school and have served at least one year's internship in an approved hospital. Candidates will then be judged on a number of qualifications, such as being a member of a specialty board, teaching connections, the number of years of professional or scientific practice, hospital or laboratory connections or a statement of military service.

The allocation of rank to successful candidates will depend on their academic age, their professional standing and their experience in the medical field. Successful candidates will then be integrated in line with medical officers of the regular Navy and assigned running mates accordingly. This means that they will be eligible for promotion along with their fellow officers of equal rank.

This law offers a fine opportunity for civilian physicians to make a career in the regular Navy and to enjoy its professional advantages as well as its retirement benefits. Physicians interested in such a career should write to the Bureau of Naval Personnel, via the Bureau of Medicine and Surgery, Navy Department, Washington, D. C.

**Medical Appointments at the State University of Iowa College of Medicine.**—Dr. Mayo Hamilton Soley has been appointed the new dean of the College of Medicine to succeed the late Dean Even M. MacEwen, who died Sept. 3, 1947, and will assume his new duties on or before July 1. Dr. William Bennett Bean has been appointed Professor of Medicine and the new head of the Department of Internal Medicine in the College of Medicine at the University of Iowa to succeed Dr. Fred M. Smith, who died Feb. 23, 1946, and will come to Iowa on or about September 1.

Dr. Soley, in addition to the deanship, will serve as the Director of Medical Services of the University Hospitals and as a Research Professor in the Department of Internal Medicine.

Dean Soley's special interests in medicine are: diseases of thyroid, respiratory physiology and anxiety states. He has published extensively in these fields. He is nationally known for his investigations on the therapeutic use of radioactive iodine in thyroid disease.

Dr. Bean is a specialist in diseases of the heart, nutrition, deficiency diseases and acclimatization to heat. His publications on these subjects in the leading medical journals of the United States since 1936 have totaled nearly forty. A portion of his research in the field of nutrition was done while he was a lieutenant in the Medical Corps of the Army of the United States during World War II. He was the winner of the John Horsley Memorial Prize in 1944. His father was for many years a distinguished anatomist at the University of Virginia Medical School.



## Book Reviews

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Electrocardiografía clínica con estudio de derivaciones unipolares. By Sergio Alvarez Mena, M.D. Price, \$10. Pp. 568. Habana, Cuba: M. Fresneda (Editor), 1947.

Even though it hasn't been the reviewer's privilege to read other books on electrocardiography written in Spanish, it would appear that Dr. Alvarez Mena has set with the publication of this textbook a pattern for other Spanish authors in the field to follow.

Through his experience as faculty instructor and as chief of the cardiology service of the Department of Medical Pathology at the University Hospital of Habana, Dr. Mena has felt the need of a suitable textbook in Spanish which would present not only what is basic and fundamental but also the new orientations and concepts on the science of electrocardiography. Equipped with adequate and generous training obtained from his teachers, Drs. F. N. Wilson, F. F. Rosenbaum, L. N. Katz, P. D. White and S. A. Levine in this country and Dr. P. D. Sodi of the National Institute of Cardiology of Mexico, the author is well qualified to do justice to the presentation.

The book is divided into twenty chapters, the first two of which are introductory notes on cardiac anatomy and physiology. In the third chapter is presented the Wilsonian concept of electrophysiology and the mechanism of production of the electrocardiographic tracing. Discussions follow on the different derivations and on the normal electrocardiogram. The author then presents a detailed study on the cardiographic waves, establishing the ranges of normality and abnormality which characterize them. A thorough discussion on electrical axis, including the mechanism of its production and methods of its determination and study, is presented and is followed by a brief and complete dissertation on the ventricular gradient in all its aspects. The next four chapters are devoted to the arrhythmias, that field in which the electrocardiogram has the final say in absolute diagnosis. These are followed by two chapters on the disturbances of auriculoventricular and intra-ventricular conduction. Dr. Mena then presents, under the subheading of "clinical electrocardiography," the alterations which accompany cardiac organic pathology in its various forms. This particular presentation is divided into four chapters, which are well organized and documented. The author finishes his book with a discussion on electrocardiographic deviations from the normal in the absence of any cardiopathy.

In a textbook of this nature, the quality of the discussion would have to be matched by the profuseness and adequacy of its illustrations. This has been more than well accomplished with the excellent diagrams and numerous electrocardiographic tracings which are included. However, for more clearness and comprehensiveness it is felt that more direct references from the text to the illustrative material should have been made. The author explains the mechanism of production of every electrocardiographic abnormality by discussing them in the light of the electrophysiologic concepts concerned.

As well as giving emphasis to practical applications of electrocardiography, this book is well printed and should receive a warm welcome from those of the medical world with command of the Spanish language.

**A History of the American Medical Association, 1847 to 1947.** By Morris Fishbein, M.D., with the biographies of the presidents of the Association by Walter L. Bierring, M.D., and with histories of the publications, councils, bureaus and other official bodies. Price, \$10. Pp. 1,226, with 169 illustrations. Cloth. Philadelphia and London: W. B. Saunders Company, 1947.

This is really several books in one. It opens with a biographic sketch of Nathan Smith Davis, the founder of the American Medical Association and continues with the history of the organization from its inception to the Centennial Meeting. Following this there are brief biographic sketches and photographs of the recipients of the Association's Distinguished Service Medal. A most remarkable section contains photographs, together with biographic notes, of each president of the organization from the first to the one hundred and first. Then comes a section devoted to the Councils and Bureaus of the American Medical Association and finally one dealing with the publications of the Association.

There are many noteworthy things between the covers of this book, and it is impossible to mention all of them. The task accomplished by Dr. Walter L. Bierring, that of collecting and publishing the photographs and sketches of one hundred and one presidents, was truly a magnificent job. The story of the Councils and Bureaus and of the publications is highly interesting. The history of the organization itself is, of course, packed with interest.

It is impossible to select from this large work any great number of portions for special mention. The serious and humorous incidents are too numerous. One might mention the agitation for reform in dress among women in 1888 and in the same year the charge that there were too many special societies. One of the most humorous sections deals with the controversy about moving the office of publication away from Chicago.

Every physician will be impressed anew at the constantly prosecuted, ever alert campaign for the improvement of medical standards and education and the fight against quackery and "patent medicines." The thoughtful physician will realize how much he owes to this organization and to its always interested officers.

**Whither Medicine: From Dogma to Science?** By Antony Fidler, M.D. Price, 6s. net. Pp. 113. Edinburgh, Scotland: Thomas Nelson & Sons, Ltd., 1947.

The writer states in his introduction that he has had no training in philosophy, but this book is purely philosophic and hence, as with all philosophic works, beyond the full comprehension of the reviewer. He believes, however, that this is a good book and that the author really has something to say which is worth while. The point seems to be that the practice of medicine should be based on methods so accurate as to approach planned experiment and to be capable of statistical analysis; if this could be pushed to its logical conclusion the physician would always know exactly the right thing to do, and the result would always be the best possible one. Dr. Fidler writes well, although one discerns everywhere that mixture of the obvious and the esoteric so common in philosophic exposition. George Henry Lewes in his "Biographical History of Philosophy" attributes to an unknown wit the definition of metaphysics as "*l'art de s'égarer avec méthode*." Be that as it may, one cannot fail to enjoy and profit from this keen and stimulating essay.

**Health Insurance in the United States.** (Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order.) By Nathan Sinai, PH.D., Odin W. Anderson, and Melvin L. Dollar. Price, \$1.50. Pp. 115. New York: Commonwealth Fund, 1946.

This small book presents one of the studies of the New York Academy of Medicine's Committee on Medicine and the Changing Order. Like the previous publications emanating from this source and published by the Commonwealth Fund, the monograph is factual and objective.

The authors divide their book into seven chapters. The first gives a rather brief introduction which devotes a paragraph or two to the various plans that have already been evolved in group insurance. The next chapter has to do with the health insurance movement from 1910 until practically the present day. A fairly long chapter is then devoted to the attitude toward health insurance of various professional, governmental and lay groups. Chapter IV is enlightening from the medicolegal viewpoint. The subsequent chapter discusses the important features of voluntary plans, and it is followed by a chapter on problems that present themselves to those who have organized and developed and are carrying through such plans. The last chapter has to do with the tremendous growth of voluntary plans, notably the Blue Cross Plan. It gives some suggestion also as to the future of health insurance in the United States.

The monograph is not long. It is well written and is easy reading, and it ought to be greatly appreciated by those who are interested in the future developments of medical practice.

**Las neumopatías aceitosas: Estudio clínico y experimental.** By Dr. Mario S. Dreyer. Pp. 128. Buenos Aires: "El Ateneo," 1946.

This monograph is an experimental and clinical study on the problem of the "oily" pneumopathies. The initial discussion is a historical outline of this pathologic entity followed by its definition and a review of the nomenclature that has been applied to the disease. The other discussion is that of the pathogenesis, classification and anatomic pathology of the condition, followed by descriptions of the symptomatology and consideration of the differential diagnosis, the course and the prognosis.

The treatment of the "oily" pneumopathies is discussed separately, and the clinical aspects of these and the other pneumopathies are considered in connection with the presentation of two illustrative case histories. The experimental study was performed in laboratory analysis (rabbits). It is introduced with the description of the artificially produced microscopic lesions. Histopathologic studies and roentgenologic findings in the "oily" pneumopathies are then presented.

The same manner of study has also been done by the author on the acute pulmonary complications projected by kerosene and on the chronic "oily" pneumopathies. A brief summary of the experimental study is then presented, including a series of conclusions as obtained from the laboratory work. Excellent photomacrographic and photomicrographic presentations are included in the discussion of the laboratory work.

It is felt that the clinical and laboratory correlation in this interesting respiratory syndrome is a contribution to the knowledge available on the disease and is an incentive toward further investigation.

**The Diagnosis and Treatment of Diarrheal Diseases.** By William Z. Fradkin, M.D. Price, \$6. Pp. 254. New York: Grune & Stratton, Inc., 1947.

This is the age of monographs, so that now one can find a book on almost any disease. The present volume is based on a different principle and deals with all the conditions featured by a certain symptom, namely diarrhea. There are chapters on diarrhea caused by protozoa, by bacteria, by mechanical factors and by glandular and other disorders. The final chapter is on diarrhea caused by miscellaneous conditions. The book really deals, therefore, with an arbitrary cross section of the whole field of medicine, rather than with any homogeneous subject. In the effort to discuss every condition in which diarrhea may be a feature, space in a small book naturally is at a premium. Cholera, for example, is disposed of in two pages, which seems brief when it is considered that a page each is given to syphilitic and gonococcic diarrheas. An outstanding feature of the book is the many excellent illustrations.

**Dermatologic Clues to Internal Disease.** By Howard T. Behrman, M.D. Price, \$5. Pp. 165, with 118 illustrations. New York: Grune & Stratton, Inc., 1947.

It is fair to say that most physicians, unless they are specialists in dermatology, are weaker in their knowledge of skin diseases than in any other phase of medicine. This interesting little book of Dr. Behrman's tries to give help by pointing out and describing the dermatologic phases of various diseases. The subject is taken up in sections, alphabetically arranged, such as acanthosis nigricans, acrocyanosis, acromegaly, acrosclerosis, Addison's disease and so on down the list. Under each heading the dermatologic implications are described. There are numerous good illustrations, and the reviewer considers this a most useful compendium.

**The Diagnosis and Treatment of Bronchial Asthma.** By Leslie N. Gay, M.D. Price, \$5. Pp. 334, with 86 illustrations. Baltimore: Williams & Wilkins Company, 1946.

Dr. Gay has covered his subject in thorough fashion and has discussed the problem of asthma in a well balanced way, with sound emphasis on the allergic aspects. There are systematic chapters on symptoms, diagnosis, etc., and the chapter on therapy exhausts every detail. There are numerous charts and illustrations, and the many case reports emphasize the points brought out in the text. The book carries all the authority which comes when one has worked personally on a subject for a long time.

**The Chest: A Handbook of Roentgen Diagnosis.** By Leo G. Rigler, M.D. Price, \$6.50. Pp. 352. Chicago: The Year Book Publishers, Inc., 1946.

The Year Book Publishers have embarked on the manufacture of a series of short handbooks dealing with roentgenologic diagnosis. This particular volume, which is listed as second in the group, considers the chest.

The author believes that the atlas method of presentation is peculiarly fitted for consideration of the thorax. He approaches the subject by an introduction which deals chiefly with methodology. Next he considers the normal chest. Finally, he takes up the various abnormal conditions which occur within the cavity of the chest.

He writes clearly, so that his various descriptions are concise. Chief emphasis, however, is laid on radiologic findings. A great many roentgenograms are hand-

somely reproduced, and each is so clearly marked that any student can easily see exactly what he should look for. The contents are well balanced; rare conditions receive but little space, while tuberculosis and malignant disease are given adequate discussion.

This is the kind of a book that students and practicing physicians like. It deserves a place in the libraries of hospitals and medical schools. Students, interns and members of hospital staffs will find the maps of this atlas of great help in charting their diagnostic course.

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#### DISCUSSION ON ARTICLE BY DRS. DASHIELL AND PALMER

(See page 173, this issue)

DR. J. EDWARD BERK, Philadelphia: Despite the incentive for early diagnosis of carcinoma of the pancreas, recognition of the disease continues to be retarded. Unfortunately, the pancreas is not easily accessible, and there are no means whereby it can be visualized roentgenologically. Moreover, all the current methods of studying the pancreas and its function do not allow for the diagnosis of carcinoma to the exclusion of all other lesions.

Data in the literature pertaining to clinical manifestations of carcinoma of the pancreas are based largely on cases in which the cancer was well advanced. These observations have tended to fix in our minds the late manifestations. Furthermore, in many of the reported cases the diagnosis was established solely by the findings at operation. The shortcomings of such unconfirmed surgical observations are obvious, especially when they are used to differentiate the clinical manifestations of pancreatic cancer confined to the head from those of cancer in the body or tail of the gland.

If more patients with pancreatic cancer are to derive benefit from the potentially curative operations now available, we must take cognizance of such reports as Dr. Dashiell's. His findings agree with ours. We must realize that pain and weight loss, altered carbohydrate metabolism and disturbed pancreatic function are important clues. We must also appreciate the value of roentgenologic examination of the pancreas by means of changes produced in neighboring viscera. Painless jaundice, palpable enlargement of the gallbladder and bulky, fatty stools, while classic and diagnostically significant, are encountered together in only a minority of the cases of pancreatic cancer.

DR. RUDOLF SCHINDLER, Los Angeles: There is one early sign of carcinoma of the pancreas which has not yet been mentioned. It is a rather reliable sign which may be present when there are no other objective findings and may be found in about one half of all cases of early carcinoma of the pancreas. It is a gastroscopic sign. When we look in the stomach, we may see a rather firm protrusion of mucosa of the antrum of the body, and, with respiration, the wall of the stomach will slide over that protrusion. If there is more pressure, the protrusion will disappear. I think that this may be an important sign in the consideration of early diagnosis.

## SPONTANEOUS MYOHEMOGLOBINURIA IN MAN

Description of a Case with Recurrent Attacks

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AND

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SPONTANEOUS myohemoglobinuria is a disease characterized by the appearance of myohemoglobin in the urine combined with evidences of muscular dysfunction and without precipitating trauma or toxic agent of apparent importance. Other myohemoglobinurias in man are those resulting from crush injuries and those associated with the ingestion of poisoned eels or fish, called Haff disease. Eight cases of spontaneous myohemoglobinuria have been reported in the literature, the first by Meyer-Betz<sup>1</sup> in 1910. The published cases were summarized by the English workers Bywaters and Dibble<sup>2</sup> in 1943, who added 1 case of their own; 2 of these cases were in the French literature and the rest in the German literature. Only in Günther's case<sup>3</sup> (1924) was the diagnosis confirmed by the necessary spectrographic studies. Since the clinical and laboratory findings in certain hemoglobinurias and in porphyrinuria may simulate those of myohemoglobinuria, the other cases remain equivocal. Louw and Nielsen<sup>4</sup> reported a case in the Scandinavian literature in 1944 in which the diagnosis was well confirmed. The patient was a 13 year old boy who had had attacks of this disease since the age of 9. The family history revealed that in five generations there had been 8 instances of progressive muscular dystrophy transmitted as a sex-linked recessive. The authors suggested

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1. Meyer-Betz, F.: Beobachtungen an einem eigenartigen mit Muskellähmungen verbundenen Fall von Hämoglobinurie, *Deutsches Arch. f. klin. Med.* **101**:85-127 (Nov.) 1910.

2. Bywaters, E. G. L., and Dibble, J. H.: Acute Paralytic Myohemoglobinuria in Man, *J. Path. & Bact.* **55**:7-15 (Jan.) 1943.

3. Günther, H.: Kasuistische Mitteilung über Myositis Myoglobinuria, *Virchows Arch. f. path. Anat.* **251**:141-149 (July) 1924.

4. Louw, A., and Nielsen, H. E.: Paroxysmal Paralytic Hemoglobinuria, *Acta med. Scandinav.* **117**:424-436, 1944.

that progressive muscular dystrophy and paralytic or spontaneous myohemoglobinuria may be related, the former being a chronic, low grade form, while the latter is an acute manifestation of the same process.

The patients ranged in age from 3 to 54 years, 5 being male and 3 female. The onset of the illness was usually sudden and sometimes accompanied with fever, nausea and vomiting. The muscles may be generally involved, or only isolated ones may be affected. There are pain, spasm and weakness, sometimes amounting to paralysis, and occasionally swelling of the afflicted muscles. The urine then becomes dark and may be nearly black, and it gives a positive reaction to the benzidine or guaiac test for occult blood. It contains albumin, creatine and yellowish pigmented casts. The disease varies in severity; the patient may die, apparently of uremia, or may recover and have many attacks. The three reported postmortem studies showed the striped muscles to be blanched, with variable degrees of degeneration, a loss of staining ability and deposition of a brownish pigment, probably myohemoglobin, in the renal tubules.

TABLE 1.—*Spectroscopic Absorption Bands*

	Maximum	Minimum	Maximum	Minimum	Maximum
Oxyhemoglobin.....	577	560	540	500	414
Oxymyohemoglobin.....	582	564	542	500	418

Cases of frank myohemoglobinuria are rare; minor degrees of it are probably more common. The present paper reports on a confirmed case, including clinical and laboratory studies. Since myohemoglobin has only recently been studied, a statement of its known properties and functions is of aid in understanding its pathologic physiology. The work of Millikan<sup>5</sup> in 1939 and that of Theorell<sup>6</sup> in 1934 furnish sound information on these points.

Myohemoglobin is a protein in the muscle sarcoplasm. It constitutes about one quarter of the total hemoglobin, and in general its properties are similar to those of blood hemoglobin. Both are combinations of protoporphyrin with iron and a specific globulin. Hemoglobin has a molecular weight of 68,000 and has four iron atoms per molecule, while myohemoglobin weighs 17,500 and contains only one iron atom. Its absorption spectrum is displaced about 4 millimicrons to the red from the principal bands of blood hemoglobin. Table 1 compares the principal absorption bands of oxymyohemoglobin and oxyhemoglobin, the data being taken from Theorell<sup>6</sup> and Heilmeyer.<sup>7</sup>

5. Millikan, G. A.: Muscle Hemoglobin, *Physiol. Rev.* **19**:503-523 (Oct.) 1939.

6. Theorell, H.: Kristallinisches Myoglobin: Die absolute Lichtabsorption von Oxy-, Carboxy-, Meta- und reduziertem Myoglobin, *Biochem. Ztschr.* **268**: 55-63, 1934.

7. Heilmeyer, L.: *Spectrophotometry in Medicine*, London, Adam Hilger, Ltd., 1943.

If oxymyohemoglobin and oxyhemoglobin are changed to the carbon monoxide forms, there occurs a displacement of their principal absorption bands to the blue; myohemoglobin shifts a maximum of 3 millimicrons and hemoglobin from 4 to 6 millimicrons.

The differences in weight of blood and muscle hemoglobin probably account for their considerable differences in renal threshold values. Hemoglobin, as has been shown by Gilligan and Blumgart<sup>8</sup> and Monke and Yuile,<sup>9</sup> averages 100 mg. per hundred cubic centimeters of plasma, while Yuile and Clark<sup>10</sup> have shown myohemoglobin to have a renal threshold of about 20 mg. per hundred cubic centimeters of plasma. It is possible to separate the two by ultracentrifugation and ultrafiltration; Bywaters and others<sup>11</sup> observed that a 9 millimicron collodin filter would permit passage of myohemoglobin and not of hemoglobin.

The chief function of myohemoglobin is as a respiratory pigment. It possesses a hyperbolic disassociation curve instead of the sigmoid curve of blood hemoglobin. Its affinity for oxygen is greater than that of blood hemoglobin and less than that of the oxidases. This property allows it to take oxygen from the blood and pass it to the cells. Furthermore, its rate of reaction with oxygen is extremely rapid, being of the order of a thousandth of a second. Citing Hill's work, Millikan<sup>5</sup> compared its affinity for oxygen to that of hemoglobin by showing that with a venous oxygen partial pressure of 40 mm. hemoglobin is 66 per cent saturated while myohemoglobin is 94 per cent saturated. After carefully considering these and other properties, Millikan concluded that myohemoglobin acts as a short time store for oxygen, tiding the muscle over from one contraction to the next.

With these facts in mind, a consideration of some related myohemoglobinurias gives a clearer understanding of spontaneous myohemoglobinuria in man. Equine paralytic myohemoglobinuria, a disease apparently identical in fundamental respects with spontaneous myohemoglobinuria in man, appears suddenly in an afflicted horse following resumption of work after a few days' rest. The horse staggers and becomes feverish, and the muscles swell and become hard and stiff. Shortly thereafter the animal passes red urine containing myohemoglobin and pigmented casts. It may recover, usually with a residual weakness,

8. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of Clinical Characteristics, Blood Metabolism, with Observations on Three New Cases and Review of the Literature, *Medicine* **20**:341-395 (Sept.) 1941.

9. Monke, J. V., and Yuile, C. L.: Renal Clearance of Hemoglobin in Dog, *J. Exper. Med.* **72**:149-165 (Aug.) 1940.

10. Yuile, C. L., and Clark, W. F.: Myohemoglobinuria: Study of Renal Clearance of Myohemoglobin in Dogs, *ibid.* **74**:187-196 (Sept.) 1941.

11. Bywaters, E. G. L.; Delory, G. E.; Rimington, C., and Smiles, J.: Myohaemoglobin in Urine of Air Raid Casualties with Crushing Injury, *Biochem. J.* **35**:1164-1168 (Nov.) 1941.



or may die from anuria due to blocking of the renal tubules by the muscle pigment. The disease is well described by Carlström<sup>12</sup> and Hutyra, Marek and Manninger.<sup>13</sup> Grzycki<sup>14</sup> stated that during an attack the animal's blood glucose, lactic acid, inorganic phosphate, creatinine and nonprotein nitrogen contents are raised while the carbon dioxide-combining power of the blood is decreased. Carlström's explanation is that there is an unduly rapid breakdown of glycogen from glycogen-rich muscles, with a resulting high production of lactic acid and direct muscular damage with release of myohemoglobin.

Stoeltzner,<sup>15</sup> Eichholtz,<sup>10</sup> Kaiserling<sup>17</sup> and Assmann and others<sup>18</sup> have described a peculiar malady called Haff disease, named after the locale in Germany, in which attacks of myohemoglobinuria in man followed ingestion of eels or fish poisoned by the discharge of the waste products of neighboring cellulose factories. The specific cause was found to be two acids in the resinous waste products, specifically pimaric and abietic.

A third type of myohemoglobinuria was studied by Bywaters and others,<sup>11</sup> being seen in some persons injured in an air raid who had been crushed beneath fallen masonry for several hours. These patients, with the restoration of circulating blood volume, passed smokey red urine which was rather acid and contained brownish casts. The urine gave a positive reaction to benzidine, and examination revealed it to have a spectrum corresponding to that of oxymyohemoglobin. The patients either recovered with a diuresis or anuria and progressive azotemia developed. Postmortem study showed areas of blanching and necrosis of the muscle together with a loss of staining ability. The kidneys had a tubular degeneration, with the deposition of brownish material which also gave a positive reaction to benzidine. The post-

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12. Carlström, B.: Ueber die Aetiologie und Pathogenese der Kreuzlähme des Pferdes (Haemoglobinaemia paralytica), *Skandinav. Arch. f. Physiol.* **61**:11-224 (March) 1931; abstracted, *Vet. Rec.* **15**:1346, 1935.

13. Hutyra, F.; Marek, J., and Manninger, R.: *Special Pathology and Therapeutics of the Diseases of Domestic Animals*, ed. 4, London, Baillière, Tindall & Cox, 1938, vol. 3, p. 133.

14. Grzycki, S.: On the Pathology and Treatment of Paralytic Hemoglobinuria in the Horse, *Berl. tierärztl. Wchnschr.* **50**:789-790, 1934.

15. Stoeltzner, W.: Untersuchungen über die Haffkrankheit, *Deutsche med. Wchnschr.* **58**:1929-1932 (Dec.) 1932.

16. Eichholtz, F.: Ursache der Haffkrankheit, *Deutsche med. Wchnschr.* **58**: 1932-1934 (Dec.) 1932.

17. Kaiserling: Die histologische Untersuchung haffkranker Katzen, *Deutsche med. Wchnschr.* **58**:1934-1935 (Dec.) 1932.

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mortem observations are similar to those described for spontaneous myohemoglobinuria in man and equine paralytic myoglobinuria in horses.

#### REPORT OF A CASE

A. D., a 39 year old white man, was admitted to the hospital for study. He stated that since childhood he had become easily fatigued and that occasionally, following slight strain, he would get cramps in the legs and weakness associated with the passage of dark urine. He could voluntarily produce such an attack by stooping or holding himself in a semicrouching position. On doing so, the anterior muscles of his thighs would become painfully contracted almost immediately and so weak that he could not stand after a half-minute. The painful spasm usually lasted one or two hours, but the pronounced weakness persisted for two weeks. He never had fever, nausea or any other general symptoms. Commencing an hour or so after the strain, his urine would darken, and this darkening would increase to a maximum around six to eight hours, generally clearing in ten hours. The urine on the next morning was always of normal color. The patient stated that after an attack he could not produce another until at least two weeks had elapsed. In recent years he had observed a slow decrease in the strength of his arms and legs and had taken a job as doorman in which little demand on his strength was made. Aside from this he had always felt well and had been accepted by the Army in 1942, although he was discharged after several months because of his ailment. Ten years before he had had a chancre and the Wassermann reaction of his blood had been positive; for this he had received rather irregular treatment for two years with arsenical and bismuth preparations.

Physical examination revealed a well nourished, intelligent man without any obvious abnormality except for weakness of the upper part of the arms and thighs together with slight wasting of the proximal limb muscles; in notable contrast were the large and strong muscles of his calves. The muscular abnormalities were sufficiently extensive to lead the visiting consultant in neurology to make a diagnosis of progressive muscular dystrophy. Routine tests of the blood and urine gave normal reactions. The reactions to the Kahn and Kolmer tests of the blood were positive, while in the cerebrospinal fluid the reactions to the Kahn and Kolmer tests, the colloidal gold curve, the protein content and the cell count were normal.

While he was in the hospital, an attack was provoked in the manner described by the patient and resulted in the production of dark urine, which was found to contain myohemoglobin. During this and three subsequent hospitalizations these observations were confirmed and extended. Additionally, he has been seen over a year and a half in the clinic. During this period he has had three spontaneous attacks similar to those described. The patient feels that his weakness has continued to progress slightly.

*Special Studies.*—1. Method of Producing an Attack: The patient assumed a position with his knees and back well flexed, in such a way as to throw a considerable strain on the extensors of the legs. He immediately began to complain of cramping pain in his thighs. In less than a minute he could no longer hold himself erect and fell to the floor. He was assisted into bed, and examination showed that the quadriceps muscles were firmly contracted and tender; they remained tender and were in spasm for nearly two hours. There was moderate spasm of the muscles of his calves. Elsewhere there were no muscular changes. There were no variations in the blood pressure, and there was no nausea, vomiting or fever. The extreme weakness disappeared within five minutes, so that the

patient was able to walk; however, some weakness persisted in the legs for several days. There was no noted swelling of the muscles. Three weeks or more had to elapse before another attack could be produced. Attempts made before this period delayed the production of the next attack.

2. Urinary Changes: The urine taken when the patient was resting was of normal yellow color and without abnormal constituents. One and a half hours after the precipitating muscular strain the urine appeared darker, and the specimens after three, six and eight hours were a dark brown mahogany color. The ten hour specimen was only slightly discolored, and that of the next morning was normal in color. Coincident with the change in color the urine became acid in  $p_H$ , and large quantities of yellowish pigmented casts, about 20 to the low power field, appeared in the centrifuged specimen. While the urine collected for twenty-four hours prior to the strain had contained less than 0.5 Gm. of albumin, the urine for the twenty-four hours after the strain contained 2.0 Gm. The specimens collected between three and ten hours after the attack gave strong reactions to the benzidine and guaiac tests for occult blood, although they contained no red cells. The urine collected for twenty-four hours prior to the strain contained 0.25 Gm. of creatine and 1.26 Gm. of creatinine, the latter being a slightly lower content than normal. Following the strain, the urine collected for twenty-four hours contained 0.94 Gm. of creatinine and 1.37 Gm. of creatine. This is a low creatinine and a high creatine content. These findings are similar to those observed in

TABLE 2.—*Chemical Studies on Urine*

	Sodium	Potassium	Creatine	Creatinine	Albumin
Twenty-four hours prior to strain	8.0 Gm.	1.5 Gm.	0.25 Gm.	1.27 Gm.	0.5 Gm.
Twenty-four hours after strain producing myohemoglobinuria .....	.....	1.7 Gm.	1.37 Mg.	0.94 Gm.	2.0 Gm.

myopathies. The results were confirmed on two other occasions. There were no significant changes in potassium level. Table 2 shows the tabulated results.

The porphyrins were assayed by the method of Dobriner and Rhoads.<sup>19</sup> The twenty-four hour urinary output after the strain was 0.065 Gm. of coproporphyrin of type III, a figure entirely within normal limits; no uroporphyrin of type III was present.

3. Spectrophotometric Identification: Specimens of urine were collected at varying intervals preceding and following the strain, and their absorption spectra were determined on a model 10s Coleman spectrophotometer and checked with the model D Beckmen spectrophotometer. Corresponding specimens of oxalated blood were taken, and spectrophotometric studies were carried out on the separated plasma. Figure 1 shows the absorption curves for the plasma and figure 2 those for the urine. Comparison with the absorption curves for the plasma of normal persons showed no significant differences. The slight oxyhemoglobin peaks were the result of unavoidable hemolysis in the handling of blood. There were no discernible myohemoglobin peaks.

With the patient resting, the urine had an absorption spectrum without any appreciable maximums or minimums, with a gradually increasing absorption from the longer to the shorter wave lengths. This is the spectrum of a normal urine. The specimens collected one-half hour after strain were essentially the

19, Dobriner, K., and Rhoads, C. P.: The Porphyrins in Health and Disease, *Physiol. Rev.* 20:416-459 (July) 1940.

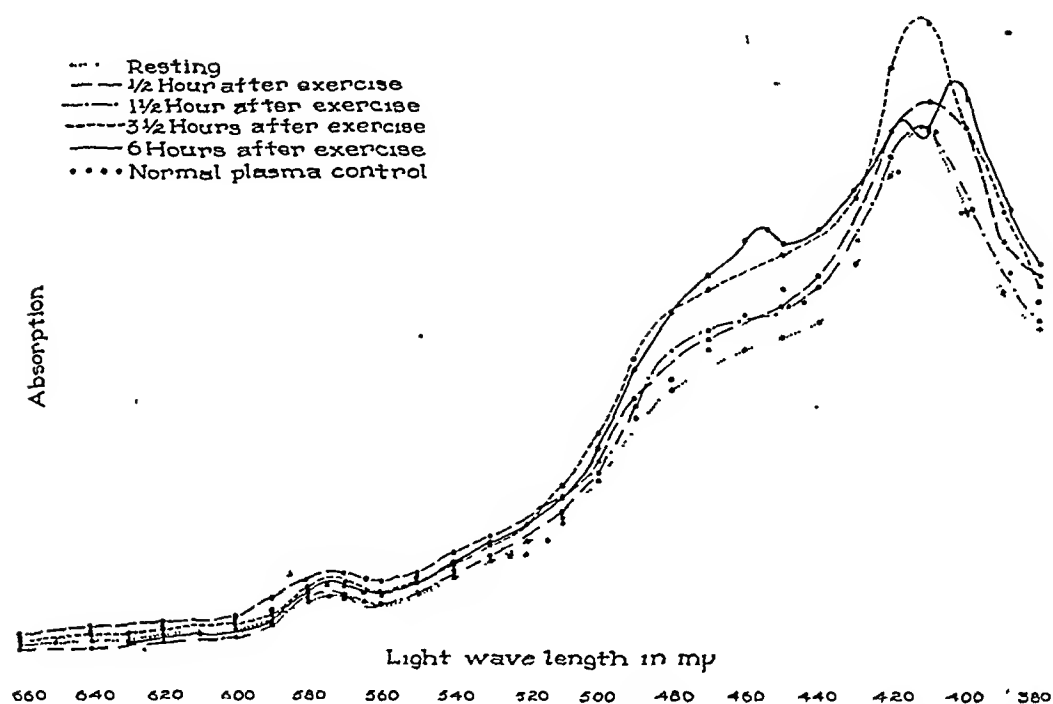


Fig. 1.—Absorption spectrums of samples of plasma in a case of spontaneous myohemoglobinuria.

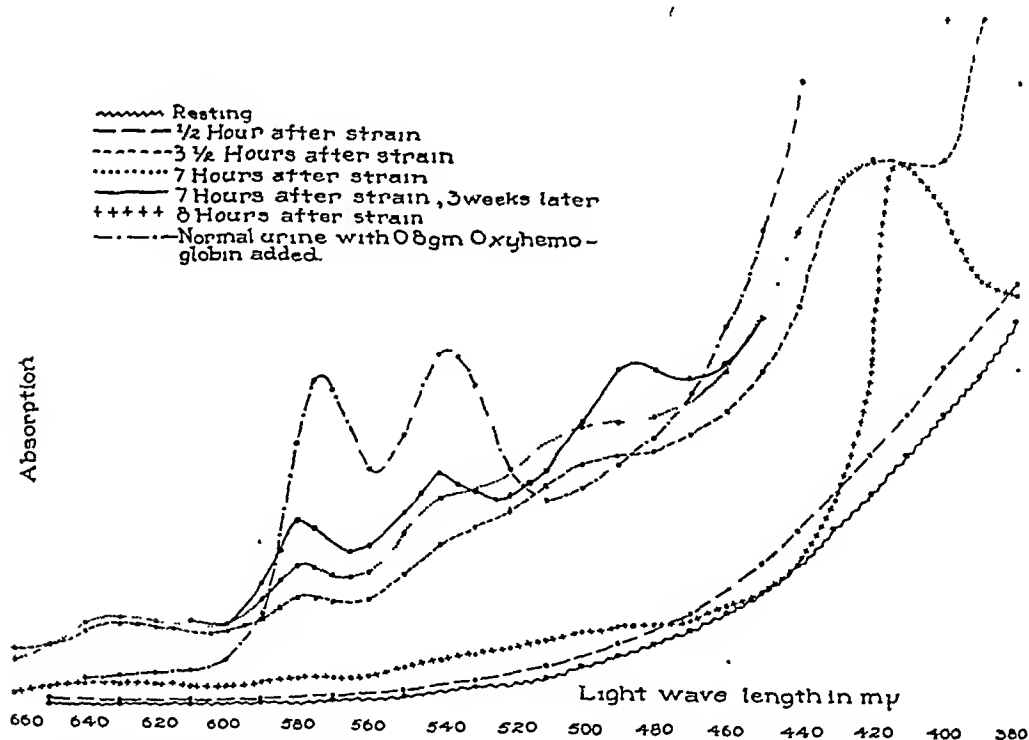


Fig. 2.—Absorption spectrums of samples of urine in a case of spontaneous myohemoglobinuria.

same. The three and a half hour and, to a greater extent, the seven hour specimens showed a well defined absorption band at 580 millimicrons, with a minimum of 565 millimicrons and a second maximum at 540 millimicrons. The substances responsible for the rising absorption from the region of 520 millimicrons toward the shorter wavelengths were not identified. The three and a half hour specimen showed a third maximum between 410 and 420 millimicrons. The eight hour voiding showed a return to nearly normal, with the exception of a strong peak at 417 millimicrons, perhaps representing metmyohemoglobin. Twenty-four hours after the strain the curve was entirely normal. The solid line curve in figure 2 represents a seven hour specimen taken three weeks later, which showed the principal oxymyohemoglobin bands even more clearly. Because of the background absorption, the absorption bands of myohemoglobin do not fall on the precise wave lengths of the purer

TABLE 3.—*Chemical Studies on Blood*

	Before Strain	After Strain							
		1 Min.	18 Min.	2 Hr.	2½ Hr.	3½ Hr.	5 Hr.	6 Hr.	24 Hr.
Protein, Gm./100 cc.*.....	6.70	....	....	...	....	....	6.50	....	6.24
	A 4.25						A 4.25		A 4.00
	G 2.45						G 2.25		G 2.24
Carbon dioxide, Vol. %....	56.8	....	....	...	52.7	....	51.8	....	57.6
Chlorides, mg./100 cc.....	620	....	....	...	650	....	660	....	653
Urea, mg./100 cc.....	17	....	....	...	...	....	....	....	18
Nonprotein nitrogen, mg./100 cc.....	25	....	....	...	26	....	26	....	25
Creatine, mg./100 cc.....	0.75	....	....	...	....	....	2.5	....	....
Creatinine, mg./100 cc.....	1.00	....	....	...	....	....	3.2	....	....
Calcium, mg./100 cc.....	9.8	....	....	...	9.8	....	10.0	....	10.0
Sodium, mg./100 cc.....	315	....	....	...	....	....	327	314	317
Potassium, mg./100 cc.....	18	....	....	...	17.0	....	15.2	20.5	20.7
Phosphorus, mg./100 cc.....	2.5	....	....	...	....	....	2.5	....	2.6
Lactic acid, mg./100 cc.....	14.3	13.9	11.7	5.7	....	9.23	....	9.4	10.0
Glucose, mg./100 cc.....	90	....	....	80	....	....	....	95	90

\* A signifies albumin; G, globulin.

solutions prepared by Theorell<sup>6</sup> but are displaced about 2 millimicrons to the blue. The dash-dot curve indicates the absorption of normal urine with added oxyhemoglobin and shows that the background shift is also true for oxyhemoglobin and, furthermore, that clear differentiation is possible between myohemoglobin and hemoglobin. Some of the specimens showed a 630 mu band, which would be expected if metmyohemoglobin were present. Saturation of the urine collected after strain with carbon monoxide displaced the principal absorption bands less than 3 millimicrons, compared with the 4 to 6 millimicrons which would be expected for oxyhemoglobin.

4. Blood Chemistry: The carbon dioxide-combining power and the sodium, potassium, chloride, lactic acid, calcium and phosphorus, serum protein, nonprotein nitrogen, urea, creatine and creatinine levels were studied. Table 3 summarizes the findings. The results of a glucose-insulin tolerance test were normal after the strain, as were those of the intravenous hippuric acid test. The plasma hemo-

globin content, determined by the method of Gilligan and others,<sup>20</sup> ranged from 5 to 15 mg. per hundred cubic centimeters, which is within the normal range. Serum taken at the height of the attack had, as determined by the method of Peters,<sup>21</sup> a creatinine content of 3.2 mg. per hundred cubic centimeters, a value nearly three times the upper limit of normal, according to Tierney and Peters,<sup>22</sup> and a creatine content of 2.5 mg. per hundred cubic centimeters, which is greatly in excess of the normal limit of 0.52 mg. set by the aforementioned authors. The results in the remainder of the tests of blood chemistry were within normal limits.

5. Other Tests: Fragility of the blood cells commenced with a 0.45 per cent concentration of sodium chloride and was complete in a 0.35 per cent solution. The Donath-Landsteiner test for a syphilitic autohemolysin gave negative reactions, as did actual chilling trials on the patient. Electrocardiographic records made before and after the myohemoglobinuria were normal. Retrograde and intravenous pyelography and other renal tests showed good function. Myohemoglobin appeared simultaneously in the urines collected through ureteral catheters during an attack.

#### DIAGNOSIS

The diagnosis of myohemoglobinuria should be considered if dark urine yielding a positive reaction for occult blood in the absence of red cells is observed in a patient in whom there is no evidence of a hemolytic disease. A level of approximately 40 mg. of hemoglobin per hundred cubic centimeters of plasma (which is well below the renal threshold of 100 mg. per hundred cubic centimeters) must be reached to give an appreciable reddish tinge to the plasma. This is a higher concentration than would be expected of myohemoglobin, with its renal threshold of 20 mg. per hundred cubic centimeters. Therefore, presumptive exclusion of the diagnosis of hemoglobinuria can be made if inspection of samples of plasma taken just prior to the appearance of dark urine does not reveal a strong reddish tinge. The association of albumin and many yellowish pigmented casts, especially if it occurs only during the acute episode, is further presumptive evidence. A positive diagnosis can be made only by identification of the characteristic absorption bands of myohemoglobin in the urine. Ultracentrifugation and ultrafiltration are of additional aid in making the differentiation from blood hemoglobin.

Clinically, the condition which might most closely simulate myohemoglobinuria is acute porphyria, of which Waldenström<sup>23</sup> has described a form associated with muscular wasting similar to progressive muscular

20. Gilligan, D. R.; Altschule, M. D., and Kalersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solution, *J. Clin. Investigation* **20**:177-187 (March) 1941.

21. Peters, J. H.: Determination of Creatinine and Creatine in Blood and Urine with Photoelectric Calorimeter, *J. Biol. Chem.* **146**:179-186 (Nov.) 1942.

22. Tierney, N. A., and Peters, J.: Mode of Excretion of Creatine and Creatine Metabolism in Thyroid Disease, *J. Clin. Investigation* **22**:595-602 (July) 1943.

23. Waldenström, J.: Neurological Symptoms Caused by So-Called Acute Porphyria, *Acta psychiat. et neurol.* **14**:375-379, 1939.

dystrophy. Even without the wasting, the combination of muscular weakness, pain in the extremities and dark urine so often seen in acute porphyria is confusing enough. Fortunately, simple laboratory tests give adequate differentiation. None of the porphyrins give a positive reaction to the benzidine or guaiac test for occult blood, nor does porphobilinogen. Myohemoglobin will not give a positive reaction to tests for porphyrinuria, nor will it give a positive reaction to Watson's<sup>24</sup> test for urinary porphobilinogen, which test usually elicits a positive reaction in acute porphyria.

The differentiation between certain hemoglobinurias and myohemoglobinuria is more readily made clinically than by laboratory tests. March hemoglobinuria is usually seen in healthy young males and consists in the appearance of dark urine containing hemoglobin, preceded by a gradual rise in plasma hemoglobin occasioned by severe exercise. As reported to date, it has been found uniformly that the exercise must be done with the patient in the erect or lordotic posture and never in a kyphotic position. The criteria of its benignity, its occurrence following severe exercise and the appearance of appreciable amounts of serum oxyhemoglobin distinguish it easily from myohemoglobinuria.

Syphilitic paroxysmal hemoglobinuria is usually precipitated by chilling, and often there is a positive Donath-Landsteiner reaction, indicating autohemolysis. Favism as a cause of paroxysmal hemoglobinuria offers no special problem in differential diagnosis. Paroxysmal nocturnal hemoglobinuria associated with chronic hemolytic anemia may be distinguished by its characteristic anemia, with thick red cells having an abnormal fragility.

#### COMMENT

The results of the studies of blood chemistry in this patient are not such as to lend any support to the theory that myohemoglobinuria is caused by rapid glycolysis or glycogen-rich muscles. Certainly there was no rise in lactic acid, inorganic phosphate or blood glucose contents or decrease in the carbon dioxide-combining power, such as were reported in equine paralytic myohemoglobinuria.<sup>25</sup> The unchanged chloride contents, carbon dioxide-combining power and sodium level indicate little change in the acid-base balance of the blood. Furthermore, if rapid glycolysis were the cause, one might be able to precipitate an attack by injecting dextrose and insulin followed by epinephrine. This was attempted in our patient, and no myohemoglobinuria resulted.

It would be of great interest to clarify some possible relation existing between spontaneous myohemoglobinuria and other diseases having

24. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, *Proc. Soc. Exper. Biol. & Med.* **47**:393-394 (June) 1941.

25. Carlström:<sup>12</sup> Hutyra, Marek and Manninger.<sup>13</sup> Grzycki.<sup>14</sup>

some similar characteristics. The porphyrin excreted in large amounts during acute porphyria is uroporphyrin of type III, which differs from the protoporphyrin of myohemoglobin in the substitution of propionyl for vinyl groups; however, these two porphyrins belong to the same isomeric system, and, theoretically, it is possible to change protoporphyrin into uroporphyrin of type III. This suggests a possible link, that of defective muscular function, between the two diseases. Extensive studies have failed to show the mechanism involved in the production of march hemoglobinuria, no abnormalities of the blood, spleen or kidneys having been implicated. It is generally assumed that the pigment involved is blood hemoglobin; however, because of the need for the most careful spectrophotometric study to distinguish it from muscle hemoglobin, it is possible that this concept is in error and that the pigment may be a type of myohemoglobin. There exists a definite possibility that certain of the primary myopathies, such as progressive muscular dystrophy, are closely related to myohemoglobinuria and may be essentially the same disease, the latter being a series of acute manifestations and the former being a continuous process. In support of this hypothesis are the similarity of muscular involvement and creatine output and the occurrence of progressive muscular dystrophy in 8 members of a family with spontaneous myohemoglobinuria described by Louw and Nielsen.<sup>4</sup>

#### SUMMARY

The literature concerning myohemoglobinuria in man is reviewed. A new case of spontaneous myohemoglobinuria, with muscular weakness and wasting similar to that in progressive muscular dystrophy, is described, the diagnosis being confirmed by spectrophotometric studies. Other studies of the blood and urine are reported.



## NEUROCIRCULATORY ASTHENIA, ANXIETY NEUROSIS OR THE EFFORT SYNDROME

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THE PURPOSE of this paper is to summarize some of the conclusions and data from a comprehensive study of patients with neurocirculatory asthenia, anxiety neurosis or the effort syndrome.<sup>1</sup> These studies were conducted over a five year period <sup>1a</sup> (1942 to 1947), for the most part on service personnel. It is intended that this summary should be of use to those who are now handling or studying problems associated with this disorder. Although most of the important investigations on the subject have been made during and immediately after wars,<sup>2</sup> the problem of neurocirculatory asthenia is important in civilian

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From the medical clinic and the Cardiac Research Laboratory of the Massachusetts General Hospital, the departments of medicine and diseases of the nervous system, Harvard Medical School, and the Fatigue Laboratory, Harvard Graduate School of Business Administration.

1. Much of the work reported here was done under a contract, recommended by the Committee on Medical Research, between the Office of Research and Development and the Massachusetts General Hospital and has been reported elsewhere in detail. The members of this project who took part in some or all of the studies were: Responsible Investigators: Dr. Paul D. White, Dr. Stanley Cobb, Director: Dr. Mandel E. Cohen, Dr. Robert E. Johnson, Captain Ashton Graybiel, U. S. N. R., Dr. William P. Chapman, Dr. Daniel W. Badal, Dr. Carl Seltzer, Jane R. Brown, Frank Consolazio, Lt. Louis J. Pecora, U. S. N. R., Mary P. Lennon, Audrey Y. Dennison and Frances Cooperstein. Others who worked on other aspects of the problem included Dr. William D. Bridges, Dr. Elwyn Evans, Dr. Edwin O. Wheeler, and Eleanor W. Reed. Other work was done and is continuing under the auspices of the Medical Research and Development Board, Office of the Surgeon General, Department of the Army.

1a. Cohen, M. E.; Johnson, R. E.; Chapman, W. P.; Badal, D. W.; Cobb, S., and White, P. D.: A Study of Neurocirculatory Asthenia, Anxiety Neurosis, Effort Syndrome: Final Report to the Committee on Medical Research, Office of Scientific Research and Development, 1946.

2. (a) Da Costa, J. M.: On Irritable Heart: A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences, *Am. J. M. Sc.* **61**:17, 1871. (b) Lewis, T.: Reports upon Soldiers Returned as Cases of "Disordered Action of the Heart (D.A.H.)" or "Valvular Disease of the Heart (V.D.H.)," *Medi-*

life. In this paper we shall emphasize the data from our studies and the conclusions of the authors and shall not attempt to summarize the abundant literature on neurocirculatory asthenia; nor will we attempt to present in detail all the studies of the project, as they are being reported in separate papers by the various workers.

In this study 144 patients, all men, were investigated thoroughly. Ninety-six per cent were from service hospitals. The average age was 26.9 years. The symptoms were multiple, with cardiovascular, respiratory, nervous and muscular symptoms predominating. This type of disorder has been variously named neurocirculatory asthenia, anxiety neurosis, effort syndrome, Da Costa's syndrome, irritable heart, disordered action of the heart, soldier's heart, vasomotor instability, vasomotor neurosis, cardiac neurosis, neurasthenia, psychoneurosis, somatization reaction general, somatization reaction psychogenic cardiovascular reaction, somatization reaction psychogenic asthenic reaction, shell shock and combat fatigue. The exact limits of any of these terms have never been clearly defined. They all refer to a type of disorder in which several of the following features are striking: nervousness, easy fatigue, shortness of breath, palpitation, spells of faintness, giddiness or apprehensiveness; poor performance in muscular work and emotional stress. However, there is an absence of any diagnosable disease of the heart, lung, nervous system or thyroid to explain these symptoms.

For purposes of comparison with the 144 patients, 105 healthy soldiers, 25 soldiers convalescent from infected war wounds and 23 soldiers convalescent from infectious hepatitis were studied.

#### CLINICAL PICTURE

Symptoms were multiple and of high incidence; those most outstanding were difficulties related to cardiovascular-respiratory function, to limitation of muscular activity and to emotional instability. At least twenty-four important symptoms occurred in 70 per cent of the cases (table 1). This is an amplification and confirmation of the description given by other authors.<sup>2</sup>

Abnormal physical findings were few. Such positive findings as there were occurred in a high percentage of cases and included high resting pulse rate, respiratory rate over 20, flushed face and neck, hyperactive knee jerks and ankle jerks and tremor of the fingers. These signs are not particularly helpful in differential diagnosis.

The results of all the routine clinical laboratory tests performed were within normal limits.<sup>1a</sup> These included hematologic studies, urinalysis, serologic test for syphilis and undulant fever, roentgen examination of the chest, gastrointestinal tract, teeth and sinuses, electrocardio-

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cal Research Committee (National Health Insurance), London, His Majesty's Stationery Office, 1917. (c) Wood, P.: Da Costa's Syndrome or Effort Syndrome, *Brit. M. J.* 1:767, 805 and 845, 1941.

graphic and electroencephalographic tests and test of the basal metabolic rate. Chemical studies on samples collected when the patients were resting gave results which were within normal limits. For blood, these included determinations of the sugar, calcium, phosphate, nonprotein nitrogen, sodium, potassium, cholesterol and chloride contents, car-

TABLE 1.—*Prevalence of Symptoms in Patients with Neurocirculatory Asthenia Compared with That in Controls*

Symptoms	Percentage Incidence			
	Patients		Controls	
	With Chronic Disease	With Acute Disease	Convalescent from Infected Wounds	Healthy
Number of subjects.....	74	25	25	55
Symptoms significantly related to effort.....	100	79	0	11
Breathlessness.....	99	79	24	13
Palpitation.....	92	82	20	15
Tires easily.....	91	93	44	7
Irritability.....	91	64	..	..
Nervousness.....	88	82	36	11
Dizziness.....	86	57	24	9
Shakiness.....	85	69	40	13
Insomnia.....	84	68	36	20
No heavy work.....	83	55	..	0
Faintness.....	82	42	20	11
Weakness.....	81	63	28	2
Apprehensiveness.....	79	56	8	2
Easily upset.....	78	63	..	7
Vascular throbbing.....	78	68	12	7
Thoracic pain (left side).....	77	61	0	5
Sweating.....	76	73	20	24
Trembling.....	74	64	36	15
Inability to get a satisfactory breath.....	74	41	16	2
Unhappiness.....	73	59	20	15
Flushes.....	73	58	20	11
Loss of weight.....	72	72	52	20
Headache.....	71	46	8	33
Attacks.....	70	72	12	2
Prolonged pain in the left side of the chest...	65	42	0	4
Nightmares.....	63	55	60	16
Panting.....	62	52	4	5
Fear of death (in attacks).....	62	52	0	5
Sighing.....	61	39	12	9
"Gas".....	59	31	4	24
Anorexia.....	55	59	23	20
Nervous chill.....	54	46	24	7
Smothering.....	50	28	8	5
Paresthesia.....	49	36	12	4
Vomiting or diarrhea.....	45	43	0	7
Attacks, no obvious stimulus.....	46	61	4	2
Attacks, apparently precipitated.....	43	32	8	0
Dry mouth.....	42	33	8	15
Urinary frequency.....	42	23	12	7
Syncope.....	41	29	24	13
Always tired.....	32	22	4	5
No light work.....	10	28	..	0
Symptoms, exclusively after effort.....	7	0	..	0

bon dioxide-combining power, carbon dioxide content and pressure  $p_H$ , oxygen content, oxygen saturation and carbonic anhydrase; for urine they included determinations of ketosteroids, thiamine, riboflavin, N<sup>1</sup>-methylnicotinamide and ascorbic acid.

On grounds of history alone two groups of patients were differentiated.<sup>3</sup> Those who had a life course of symptoms of neurocirculatory

3. Cohen, M. E.: Bull. Cardiovascular Diseases, p. 7, National Research Committee, Division of Medical Sciences acting for the Committee on Medical Research of the Office of Scientific Research and Development, 1944.<sup>6</sup>

asthenia or those who could never do hard work or athletics were designated as having "chronic neurocirculatory asthenia." Those who gave convincing evidence of good health, ability to do muscular work or athletics and nervous stability previous to the onset of illness were designated as having "acute neurocirculatory asthenia." Although this classification was based in every instance on history alone, nevertheless in all the quantitative studies mentioned in the following paragraphs which yielded significant differences between healthy controls and patients with neurocirculatory asthenia, mean values for those with the acute form of the disease fall between those for the healthy controls and those for the patients with the chronic form of the disease.

#### STUDIES OF MUSCULAR WORK

Patients and controls were studied during and after muscular work.<sup>4</sup> Moderate work consisted of walking on a treadmill,<sup>5</sup> and hard work consisted of running on a treadmill,<sup>5</sup> stepping up and down on a 20 inch (50.8 cm.) step<sup>6</sup> and stepping up and down with a pack on the back.<sup>7</sup>

Table 2 shows that in the basal condition the pulse and respiratory rates are slightly abnormal in neurocirculatory asthenia. However, there was no difference between patients with neurocirculatory asthenia and controls in regard to oxygen consumption and the blood lactate concentration while resting.

Although differences at rest were not great, during muscular work striking abnormalities appeared. One might ask what the characteristics are of a man in good condition for muscular work.<sup>8</sup> Important features are (1) his ability to take up a high amount of oxygen rapidly, (2) his ability to do a given amount of work with less displacement of his physiologic mechanisms than the average and (3) his ability

4. Cohen, M. E.; Johnson, R. E.; Cobb, S.; Chapman, W. P., and White, P. D.: Studies of Work and Discomfort in Patients with Neurocirculatory Asthenia, *J. Clin. Investigation* **23**:934, 1944.

5. (a) Robinson, S.: Experimental Studies of Physical Fitness in Relation to Age, *Arbeitsphysiol.* **10**:251, 1938. (b) Johnson, R. E.; Brouha, L., and Darling, R. C.: A Test of Physical Fitness for Strenuous Exertion, *Rev. canad. de biol.* **1**:491, 1942.

6. Brouha, L.; Graybiel, A., and Heath, C. W.: The Step Test: Simple Method of Measuring Physical Fitness for Hard Muscular Work in Adult Man, *Rev. canad. de biol.* **2**:86, 1943.

7. A "Pack" Test of Physical Fitness for Hard Muscular Exercise, Report no. 1, Office of Scientific Research and Development, Boston, Harvard Fatigue Laboratory, April 13, 1942. Darling, R. C.; Johnson, R. E.; Pitts, G. C.; Consolazio, F. C., and Robinson, P. F.: Effects of Variations in Dietary Protein on the Physical Well Being of Men Doing Manual Work, *J. Nutrition* **28**:273, 1944.

8. Robinson, S.; Edwards, H. T., and Dill, D. B.: New Records in Human Power, *Science* **85**:409, 1937. Data recalculated.

TABLE 2.—*Subjects with Neurocirculatory Asthenia Compared with Controls*  
(*Basal Values, Values After Moderate Work and Values*  
*After "Exhausting" Work*)\*

	Patients with Neurocirculatory Asthenia						Healthy Controls	
	Total		Chronic		Acute			
	No.	Value	No.	Value	No.	Value	No.	Value
Resting								
Pulse rate.....	49	79	..	....	..	....	55	71
Respiratory rate.....	50	15.8	..	....	..	....	34	13.2
Basal metabolic rate.....	50	+ 4	..	....	..	....	34	+ 1
Ventilation—liters per square meter per minute.....	50	4.53	..	....	..	....	34	4.77
Blood lactate—mg./100 cc.....	50	12.6	32	11.8	18	13.9	23	16.2
Moderate Exercise								
Walking at 3.5 miles per hour at 8.9 per cent grade								
Maximum pulse rate.....	25	161	..	....	..	....	20	150
Ventilation—cc./kilogram per minute .....	20	657	..	....	..	....	20	574
Oxygen consumption—cc./kilo- gram per minute.....	20	28.6	..	....	..	....	20	28.8
Ventilatory efficiency.....	20	4.46	..	....	..	....	20	5.08
Blood lactate—mg./100 cc.....	61	41.1	42	44.6	19	33.6	41	21.0
Blood sugar—mg./100 cc.....	22	111	..	....	..	....	18	107
"Exhausting" Exercise								
Step test—20 inch step (30 steps per minute)								
Maximum Effort								
Duration .....	94	109	71	100	23	136	40	190
Sum of three recovery pulse rates	94	369	71	369	23	371	40	356
"Index of fitness".....	94	30	71	28	23	86	40	59
Running 7.0 miles per hour at 8.9 per cent grade								
Maximum Effort								
Duration .....	69	92	55	84	14	125	60	202
Sum of three recovery pulse rates	60	420	46	418	14	424	35	403
"Index of fitness".....	60	22	46	19	14	31	35	50
Lactate 5 minutes after—mg./100 cc. of blood.....	68	94	50	93	18	100	46	118
Ventilation—cc./kilogram per minute .....	19	1,082	..	..	..	...	20	1,299
Oxygen consumption—cc./kilo- gram per minute.....	18	39.5	..	..	..	...	20	46.9
Ventilatory efficiency.....	18	4.35	..	..	..	...	20	5.44
For the same duration								
Ventilation—cc./kilogram per minute during								
0 to 1.....	20	829	..	..	..	...	20	645
1 to 2.....	20	1,037	..	..	..	...	20	977
2 to 3.....	20	1,108	..	..	..	...	20	1,216
Oxygen consumption—cc./kilo- gram per minute during								
0 to 1.....	18	33.8	..	..	..	...	20	35.0
1 to 2.....	13	40.0	..	..	..	...	20	43.9
2 to 3.....	7	37.7	..	..	..	...	19	46.5
Ventilatory efficiency during								
0 to 1.....	18	4.29	..	..	..	...	20	5.42
1 to 2.....	13	3.38	..	..	..	...	20	4.59
2 to 3.....	8	3.46	..	..	..	...	19	3.92
Lactate—mg./cc. per second of test time.....	68	1.31	50	1.48	18	0.85	46	0.46

\* Basal refers to supine, resting and fasting states; moderate work refers to the treadmill walk—3.5 miles per hour at 8.9 per cent grade, and "exhausting" work refers to the treadmill run—7.0 miles per hour at 8.9 per cent grade. The run is for a maximum of 5 minutes or until the patient's stopping point. Ventilatory efficiency = oxygen consumption ÷ pulmonary ventilation. "Index of fitness" = duration of hard work test ÷ sum of three recovery pulse rates.

to achieve and tolerate as a result of maximal work a great displacement of physiologic mechanism.

Patients with neurocirculatory asthenia showed poor ability to take up oxygen (fig. 1) during hard work and a large displacement for a moderate amount of work (table 2), and they never accomplished maximal work giving great displacement. In other words, they were diametrically opposite to the man in good condition for muscular work.<sup>4</sup>

In order to compare physiologic responses during work in patients with neurocirculatory asthenia and in controls, a task was chosen which could be finished by both. A treadmill walk was used for this purpose. After moderate exercise of fixed duration and amount, patients with neurocirculatory asthenia showed higher pulse rates and higher blood lactate concentrations (table 2) than controls.<sup>9</sup> Pulmonary ven-

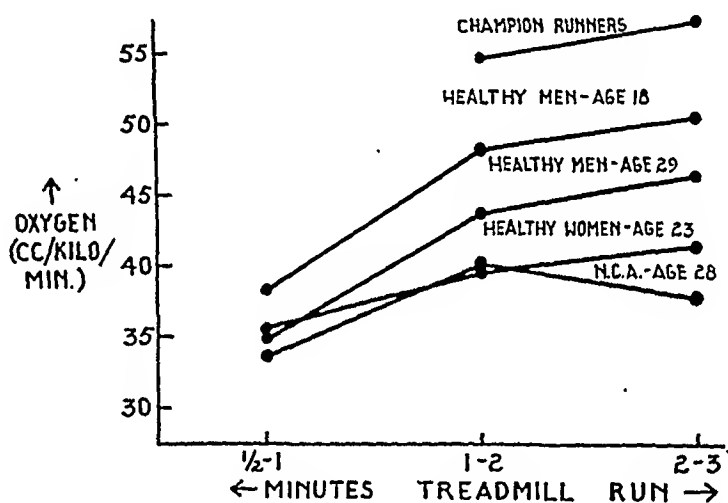


Fig. 1.—Oxygen consumption during hard work. All subjects ran at seven miles per hour up a grade of 8.9 per cent for the time shown in the abscissa. Ordinates show average oxygen consumption in cc. per kilogram of body weight per minute for 4 champion distance runners (9), 77 healthy men aged 18 years (12), 20 healthy men aged 29 years (13), 17 healthy women aged 23 years (14) and 20 patients with neurocirculatory asthenia aged 28 (10). The figure shows throughout that the poor work groups, the older men, the women and the patients have the lowest consumption.

tilation was higher in the patients and oxygen consumption was the same in the two groups, giving lower ventilatory efficiency in the former while they were walking.

In hard work tests, patients did not last as long as did control subjects. The subjects were instructed to go for a full five minutes or for as long as they could. The average duration for patients with the chronic form of the disease on a treadmill run was eighty-four seconds and for those with the acute form of the disease it was one hundred and twenty-five seconds, as compared with two hundred and two

9. Cohen, M. E.; Consolazio, F. C., and Johnson, R. E.: Blood Lactate Response During Moderate Exercise in Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome, *J. Clin. Investigation* 26:339, 1947.

seconds for control subjects. Similar results were obtained in the step test. For patients with chronic neurocirculatory asthenia the stopping point was reached in one hundred seconds, for those with the acute form it was reached in one hundred and thirty-six seconds and for the controls it was reached in one hundred and ninety seconds.

It will be noted that the sum of three recovery pulse rates is slightly higher for the patients than for the control subjects despite the fact that the duration of the run performed by the former was much shorter. The "index of fitness,"<sup>5b</sup> calculated by dividing the duration of the run by the sum of the three recovery pulse rates, is therefore low in neurocirculatory asthenia. The maximum lactate concentration after hard work is not as high. This is misleading, since the patient probably does not perform long enough to raise the blood lactate level. When the time of performance is considered, however, it can be seen (table 2) that as calculated in amount of lactate per cubic centimeter of blood per second of running time the lactate concentration in neurocirculatory asthenia is more than double that of the healthy subject, i. e., 1.31 as compared to 0.60 mg. The patient with chronic neurocirculatory asthenia has the greatest concentration of lactate per unit of time; the patient with the acute form of the disease is intermediate between the control subject and the patient who is chronically affected. Physiologic responses to maximum effort in hard work tests are not strictly comparable since the duration of maximal performance is not the same for each person. However, for the first two minutes of the run and in a few instances for the third minute it was possible to record measurements for patients with neurocirculatory asthenia who lasted for that time and to compare them with those for the healthy control subjects during the same interval. Striking differences were noted. During this run, oxygen consumption and ventilatory efficiency were lower in the patients than in the healthy controls. At first it may seem surprising that the patients used less oxygen during running,<sup>10</sup> as this might suggest high mechanical efficiency. Actually this is part of a general pattern, as can be seen from figure 1, since champion runners<sup>8</sup> use most oxygen, healthy men use less, young men<sup>11</sup> using more than older men,<sup>12</sup> women less than this<sup>13</sup> and finally patients with neuro-

10. Cohen, M. E.; Johnson, R. E.; Consolazio, F. C., and White, P. D.: Low Oxygen Consumption and Low Ventilatory Efficiency During Exhausting Work in Patients with Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis, *J. Clin. Investigation* **25**:292, 1946.

11. Heath, C. W., and others: *What People Are: A Study of Normal Young Men*, Cambridge, Mass., Harvard University Press, 1945. Heath, C. W.: Unpublished data.

12. Harvard Fatigue Laboratory: Unpublished data.

13. Metheny, E.; Brouha, L.; Johnson, R. E., and Forbes, W. H.: Some Physiologic Responses of Women and Men to Moderate and Strenuous Exercise: A Comparative Study, *Am. J. Physiol.* **137**:318, 1942.

circulatory asthenia<sup>10</sup> the least. This fact of low oxygen consumption during hard work together with high lactate concentration suggests abnormal aerobic metabolism and high anaerobic metabolism.

In general, when one compares groups of subjects who work hardest and longest on these tests with those who work least, i. e., women, men in poor training<sup>14</sup> and patients with neurocirculatory asthenia,<sup>1</sup> differences between the two groups become more apparent as the intensity and duration of the work tests are increased.

In other words, the more the work is stepped up the more clearly does the "poor work group" separate itself from the "good work group." When the subjects are at rest the measurable differences are few and small. During moderate exercise, measurable differences appear consistently. In groups whose performance during hard work tests, i. e., running, is of short duration walking is associated with high blood lactate concentration, high pulse rate, high pulmonary ventilation and low ventilatory efficiency. However, average oxygen consumption is the same for all groups during the walk.

During the portion of a hard work test which all subjects perform for a comparable length of time at a fixed pace and grade, all the differences seen in walking are accentuated. In addition, oxygen consumption is lowest in the groups who do not run well (fig. 1).

When subjects run at a fixed pace until they reach their stopping point, those who run longest have higher oxygen consumption, higher pulmonary ventilation, higher blood lactate levels, higher ventilatory efficiency and lower pulse.

In other words, during work of the same duration regardless of the intensity the "poor work group" showed the greatest physiologic displacements except for oxygen consumption. With regard to hard work, carried out to the point at which the subjects stopped running, the "good work groups" ran longest and reached the greatest levels of physiologic displacements. These observations may seem to be contradictory; they are not, however, if one realizes that the "good work group," as exemplified by outstanding athletes, perform longer and harder tasks while undergoing maximum physiologic displacements. During moderate work comparable to that done by other persons they show less physiologic change.

We concluded from this study that with either moderate or "exhausting" muscular work, during which patients and controls alike perform for the same duration and at the same rate, there are many measurable abnormalities in patients with neurocirculatory asthenia. All the findings in table 2 are consistent with the hypothesis that aerobic metabolism is abnormal in these patients. This is strikingly illustrated in

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14. Knehr, C. A.; Dill, D. B., and Neufeld, W.: Training and Its Effects on Man at Rest and at Work, *Am. J. Physiol.* 136:148, 1942.



figure 1, and the high blood lactate concentration demonstrates a reciprocal high oxygen debt.

It cannot be stated whether these findings apply specifically to patients with neurocirculatory asthenia or whether they are the general signs of poor health, chronic illness, poor runners or poor state of training.

English workers in 1943 concluded from studies of lactic acid levels in the effort syndrome<sup>15</sup> that the patients "showed . . . no major biochemical abnormality in their response. The  $p_H$  and lactate were

TABLE 3.—*Incidence in Neurocirculatory Asthenia of Symptoms Involving Breathing\**

Group Studied	Patients		Controls	
	With Chronic Disease	With Acute Disease	Convalescent	Healthy
Number of subjects.....	74	25	25	55
From present illness				
1. Breathlessness.....	99	79	24	13
2. Inability to get a satisfactory breath....	74	41	16	2
3. Panting.....	62	52	4	5
4. Sighing.....	61	39	12	9
5. Gas mask trouble.....	55	17	12	15
6. Smothering.....	50	28	8	5
From past history				
7. Trouble breathing in water (while swimming).....	75	22	12	10
8. Always short of breath.....	41	0	8	7
During hard work test				
Number of subjects.....	..	65	..	31
9. Breathlessness severe enough to cause patients to stop.....	..	62	..	18

\* Significance of differences in incidence of symptoms; patients with chronic disorder versus healthy controls—all differences significant; patients with chronic disorder versus those with acute disorder—all differences significant except for 3, 4 and 6; patients with chronic disorder versus convalescent controls—all differences significant; patients with acute disorder versus convalescent controls—all differences significant except 2, 5, 6 and 7; patients with acute disorder versus healthy control subjects—all differences significant except for 5 and 7, and convalescent control subjects versus healthy control subjects—significant difference shown only with regard to number 2.

in keeping with the amount of work done . . ." and, further, that the patients' difficulty was simply a matter of lack of "persistence." Our findings, reported in 1944,<sup>4</sup> of abnormally high blood lactate concentration evidencing abnormal oxygen debt made this conclusion untenable. Our later work provided further evidence of abnormal aerobic metabolism.<sup>16</sup> In work reported in 1946 the English workers revised their previous conclusions and found definite chemical abnormalities in neurocirculatory asthenia, and their finding of high oxygen consump-

15. Jones, M., and Scarisbrick, R.: Effort Intolerance in Soldiers: Review of Five Hundred Cases, War Med. 2:901 (Nov.) 1942.

16. Cohen and others.<sup>1a</sup> Cohen, Johnson, Consolazio and White.<sup>10</sup>

tion in the recovery period<sup>17</sup> is an important addition to our general concept as expressed here and elsewhere.<sup>1a</sup>

#### STUDIES OF BREATHING AND DYSPNEA

Patients with neurocirculatory asthenia commonly complain of shortness of breath, inability to draw a satisfactory breath and inability to do hard work because of breathlessness. The incidence of symptoms involving breathing is given in table 3, which shows significant differences between patients and controls. The incidence is higher among patients with chronic illness than among those with the acute form and higher among convalescent controls than among healthy controls.

Quantitative studies of respiration showed that while resting and breathing oxygen patients with neurocirculatory asthenia have more rapid respiratory rates and more shallow breathing than do healthy control subjects.

The ventilation index<sup>18</sup>

$$V. I. = \frac{\text{Ventilation}}{\text{Vital capacity}} \times \left( 1 + \frac{\text{ideal weight}}{\text{actual weight}} \right) \frac{1}{2}$$

was abnormally high in patients for all four speeds of exercise. This was due to a high ventilation factor and not to vital capacity, which was normal in our series of patients.<sup>1a</sup> (The mean vital capacity for 54 healthy men was 2,387 cc. per square meter of body surface and for 73 patients with neurocirculatory asthenia 2,362 cc.).

The ventilation index is usually an objective correlate of the subjective phenomenon of dyspnea. As shown in figure 2, when the level of ventilation index was the same, more of the patients than of the healthy controls complained of dyspnea. Furthermore, the degree of dyspnea complained of was greater in patients than in healthy controls doing the same amount of exercise and with the same ventilation index. Further details have been reported by Cohen and White.<sup>18a</sup>

#### CARDIOVASCULAR STUDIES

Cardiovascular studies showed only a few significant deviations from the normal.

The pulse rate at rest, during exercise and after exercise was high, averaging 8 to 10 beats per minute higher than that in healthy controls.

17. Jones, M., and Mellersh, V.: A Comparison of the Exercise Responses in Anxiety States and Normal Controls, *Psychosom. Med.* 8:180, 1946.

18. Harrison, T. R.; Turley, C. F.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: The Measurement of Ventilation as a Test of Cardiac Function, *Arch. Int. Med.* 48:377 (Sept.) 1931.

18a. Cohen, M. E., and White, P. D.: Studies of Breathing, Pulmonary Ventilation and Subjective Awareness of Shortness of Breath (Dyspnea) in Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis, *J. Clin. Investigation* 24:520, 1947.

In our series the size of the heart, as determined from measurements of the diameter and area of the heart in roentgenograms, was not significantly different in the two groups (50 subjects in each group). Our findings are described elsewhere<sup>19</sup> and do not confirm the conclusion of others<sup>20</sup> that neurocirculatory asthenia is characterized by the presence of a small heart. The electrocardiogram, made with the patient at rest and after mild exercise (Master's test), was within normal limits.<sup>21</sup>

Other normal findings were related to responses of the blood pressure and the pulse to changes of posture on a tilt table, resting venous pressure, blood volume, vital capacity, circulation time and resting cardiac output as measured by the acetylene method of Grollman and compared with normal standards.<sup>22</sup> Measurement of the cardiac output by the direct Fick method employing catheterization of the right





DYSPNEA →	 NONE	 SLIGHT	 MODERATE	 SEVERE
CONTROLS	63%	28%	8%	1%
PATIENTS	6%	36%	44%	14%

Fig. 2.—Dyspnea (at ventilation index of 15 to 25). The ventilation index of Harrison<sup>18</sup> is said to be an objective correlate of the subjective phenomenon of dyspnea. This shows that the incidence and severity of dyspnea in neurocirculatory asthenia are out of proportion to the ventilation index as well as to the severity of the exercise described previously.

auricle of the heart<sup>23</sup> gave mean values that were within the limits of those reported by Stead and his associates<sup>24</sup> for normal subjects with

19. Carlotti, J.; Cohen, M. E., and White, P. D.: The Heart Size in Neurocirculatory Asthenia, Effort Syndrome or Anxiety Neurosis, *Am. Heart J.* **34**: 552, 1947.

20. Master, A. M.: Neurocirculatory Asthenia Due to Small Heart, *M. Clin. North America* **28**:577, 1944.

21. White, P. D.; Cohen, M. E., and Chapman, W. P.: The Electrocardiogram in Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome, *Am. Heart J.* **34**:390, 1947.

22. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, Publisher, 1932. Burwell, C. S., and Strayhorn, W. D.: Concretio Cordis: Clinical Study, with Observations on Venous Pressure and Cardiac Output, *Arch. Surg.* **24**:106 (Jan.) 1932.

23. Cournand, A.: Measurement of the Cardiac Output in Man Using the Right Heart Catheterization, *Federation Proc.* **4**:207, 1945.

24. Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization: Normal Values with Observations on the Effect of Anxiety and Tilting, *J. Clin. Investigation* **24**:326, 1945.

"evidence of anxiety." Our patients seemed tense and apprehensive during the procedure. Values obtained by the Grollman method were lower than those obtained by the direct Fick method.<sup>24</sup>

Ballistocardiographic studies were done on 30 patients. We were not able to satisfy ourselves as to the reliability or the theoretic soundness of this method in its present state of development as applied to the measurement of cardiac output in patients, and we are in agreement with Cournand, Hamilton, and others in their cautious evaluation of the method.<sup>25</sup>

One of the positive findings in patients with neurocirculatory asthenia was the structure of the capillaries of the finger nail folds described in a report by Cobb, Cohen and Badal.<sup>26</sup> Table 4, composed from that work, shows the result of visual examination of the nail fold with a capillary microscope. Control subjects for the most part had capil-

TABLE 4.—*Capillary Types in the Finger Nail Folds of Patients with Neurocirculatory Asthenia and of Controls*<sup>26</sup>

Group of Subjects	Number of Subjects	Percentage Prevalence*	
		Simple Loops	Complex Loops
Patients with neurocirculatory asthenia (chronic).....	32	44	56
Patients with neurocirculatory asthenia (acute).....	16	47	53
Controls (healthy).....	23	79	21
Controls (osteomyelitis).....	21	65	35

\* The difference in incidence of simple loops is statistically significant as between patients with neurocirculatory asthenia and healthy controls and between controls with osteomyelitis and healthy controls. The same is true for the incidence of complex loops.

laries of a simple U type (simple loops), whereas patients with neurocirculatory asthenia had predominantly crossed loop, twisted or dentate and crenate forms (complex loops). We do not know whether this difference represents an abnormality which could be demonstrated in fixed microscopic sections. The difference between the two types of controls, i. e., healthy men and men with infected wounds, suggests that these abnormalities are not restricted to patients with neurocirculatory asthenia but may occur in other conditions.

#### STUDIES OF PAIN AND DISCOMFORT

Common among symptoms of neurocirculatory asthenia are pain in the chest, gastrointestinal pain, indigestion, headaches and excessive

25. Hamilton, W. F.: Notes on the Development of the Physiology of Cardiac Output, *Federation Proc.* 4:183, 1945. Cournand.<sup>23</sup>

26. Cobb, S.; Cohen, M. E., and Badal, D. W.: Capillaries of the Nail Fold in Patients with Neurocirculatory Asthenia (Effort Syndrome, Anxiety Neurosis), *Arch. Neurol. & Psychiat.* 56:643 (Dec.) 1946.

self observation, i. e., symptoms involving discomfort (table 1). Therefore an investigation was made of the patients' perception of painful stimuli and their reaction to an endurance of these.

Thermal stimuli consisted of a beam from a hot lamp in the Hardy-Wolff radiation apparatus shining for three seconds on the blackened forehead.<sup>27</sup> The level at which thermal stimulus was perceived as painful was not significantly different when patients and controls were tested. However the level at which the subject winced, i. e., reacted, was lower for patients than for 44 controls (0.364 Gm. calories per second per square centimeter). As the stimulus became stronger, some subjects pulled their heads away from the apparatus. This occurred most frequently and at the lowest levels when patients with chronic neurocirculatory asthenia were being tested. This work has been reported in detail by Chapman, Cohen and Cobb<sup>28</sup> and the relation of the responses to the symptom "nervousness" pointed out.

The response to the discomfort of sustained hand gripping was tested by means of a hand dynamometer, the use of which has been described by others.<sup>29</sup> The patients' maximum grasp was determined in each hand by duplicate trials.<sup>29a</sup> The dynamometer was then set at 60 per cent of the subject's maximum grasp, and the subject was asked to hold it at this level as long as he could. There was no significant difference in maximum grip strength between patients with neurocirculatory asthenia and healthy controls. However, duration of gripping at 60 per cent of the maximum was significantly less for 58 patients with chronic neurocirculatory asthenia (thirty-six seconds) than for healthy controls (forty-eight seconds).

The patients' response to pain and discomfort corresponds well with the complaints which they make and which others make about them that stimuli and situations which involve discomfort or endurance are not handled well.<sup>29a</sup>

#### PSYCHOLOGIC TESTS<sup>30</sup>

Psychologic tests<sup>31</sup> were administered in order to collect quantitative evidence bearing on three questions.

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27. Cohen, M. E., and White, P. D.: Progress Report, Committee on Medical Research, Office of Scientific Research and Development, July 1944. Cohen, Johnson, Cobb, Chapman and White.<sup>4</sup>

28. Chapman, W. P.; Cohen, M. E., and Cobb, S.: Measurements of Levels of Heat Stimulus Perceived as Painful and Producing Wince and Withdrawal Reactions in Patients with Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome and in Control Subjects, *J. Clin. Investigation* 25:890, 1946.

29. Dunlap, J. W.: Tests of the "Ability to Take It," Report no. 11, Civil Aeronautics Administration, Division of Research, February 1943.

29a. Cohen and others.<sup>1a</sup> Cohen, Johnson, Cobb, Chapman and White.<sup>4</sup>

30. Tests were administered and analyzed for the most part by Jane R. Brown and Audrey Y. Dennison.

31. Cohen, and White.<sup>27</sup> Cohen and others.<sup>1a</sup>

1. Are patients with neurocirculatory asthenia normally intelligent? Scores in the Wechsler-Bellevue<sup>32</sup> tests (54 cases) were within average limits, the mean for the intelligence quotient being 107.2 for the verbal score and 103.2 for the performance score.

2. Was the patients' disability related to an unusual attitude toward war? Thurstone's "war attitude test"<sup>33</sup> was administered to 74 patients with neurocirculatory asthenia, 47 healthy soldiers, 25 convalescent wounded soldiers and 36 conscientious objectors. The scores of the patients and of the control soldiers were the same and placed them in the "neutral" category. In contrast, the scores of the conscientious

TABLE 5.—*Comparison of Patients with Neurocirculatory Asthenia and Controls in Three "Neurosis Tests"*

Test and Component of Test	Patients		Controls	
	With Chronic Disease	With Acute Disease	Convalescent	Healthy
I. Psychosomatic inventory (36)				
Physiologic score				
Mean percentage ratings.....	7.6	15.2	41.7	58.8
Normal scale				
Psychologic score				
Mean percentage ratings.....	26.2	29.1	54.2	56.8
Normal scale				
Number of subjects.....	72	34	23	56
II. Personality inventory (37)				
Mean score.....	62	56	....	32
Neurotic category				
Number of subjects.....	72	29	....	54
III. Multiplex personality inventory (38)				
Mean score				
Hysteria.....	75.6	67.1	55.8	47.1
Depression.....	74.0	71.7	56.5	48.6
Hypochondriasis.....	73.9	67.7	54.2	50.7
Psychasthenia.....	64.0	57.4	53.6	47.3
Number of subjects.....	51	29	24	55

objectors placed them in the "strongly pacifistic category." None of the soldiers had scores which placed them in the "militaristic" categories, which corresponded with a general impression of lack of "militaristic" feelings in the American Army.<sup>1a</sup>

3. Do psychologic tests whose scores do not depend on the observers' bias confirm the clinical impression that neurocirculatory asthenia properly belongs to the group called by others "neurosis"? Three questionnaire tests were administered, namely, the psychosomatic inventory,<sup>34</sup>

32. Wechsler, D.: *The Measurement of Adult Intelligence*, ed 2, Baltimore, Williams & Wilkins Company, 1941.

33. Thurston, L. L.: *Attitude Toward War Scale*, Chicago, University of Chicago Press, 1930.

34. McFarland, R. A., and Seitz, C. P.: *A Psychosomatic Inventory*, J. Applied Psychol. 22:327, 1938.

the personality inventory<sup>35</sup> and the multiphasic personality inventory.<sup>36</sup> Table 5 shows that in each of the three tests patients with neurocirculatory asthenia obtain scores which place them in the neurosis category. In addition, patients with the acute form are less abnormal than those with the chronic form. Convalescent controls obtained scores which in all instances tended in the direction of the "neurosis scores," probably because some symptoms like those of "anxiety neurosis" are sometimes found (table 1) in normal convalescence.<sup>37</sup> However, this does not mean that normal convalescence and neurosis are identical.<sup>38</sup> The exact meanings of these tests are not clear.

In addition, 22 patients were given the thematic apperception test<sup>38a</sup> in order to test out the usefulness of a so-called projective test. Results of tests scored by three different observers did not give impressive agreement. This, taken with the fact that the test involved unproved assumptions, made its usefulness of doubtful value in our hands.

TABLE 6.—*Incidence of Neurocirculatory Asthenia in Relatives of Patients with Chronic Neurocirculatory Asthenia and of Healthy Control Subjects*

	Patients (67 Families)	Healthy Controls (54 Families)
Fathers.....	18.5%	0%
Mothers.....	58.0%	0%
Brothers and sisters.....	12.6%	0%
Total number of relatives about whom satisfactory information was obtained		
Fathers.....	50%	54%
Mothers.....	58%	54%
Brothers and sisters.....	109%	175%

#### FAMILIAL PREVALENCE OF NEUROCIRCULATORY ASTHENIA

A study was made of familial prevalence for two reasons: first, a high proportion of patients stated that symptoms similar to their own occurred in other members of the family; secondly, earlier writers have touched on the possibility that this disorder may be hereditary.<sup>39</sup>

35. Bernreuter, R. G.: *Manual for the Personal Inventory*, Stanford University, Calif., Stanford University Press, 1938.

36. McKinley, J. C., and Hathaway, S. R.: *The Identification and Measurement of the Psychoneuroses in Medical Practice: The Minnesota Multiphasic Personality Inventory*, J. A. M. A. **122**:161 (May 15) 1943.

37. Cohen, M. E., and White, P. D.: *Progress Report, Committee on Medical Research, Office of Scientific Research and Development, December 1944*. Cohen and others.<sup>1a</sup>

38. Brodman, K.; Mittelman, B., and Wolff, H. G.: *Psychologic Aspects of Convalescence*, J. A. M. A. **129**:179 (Sept. 15) 1945.

38a. Murray, H. A.: *Thematic Apperception Test*, Cambridge, Mass., Harvard University Press, 1942.

39. Beard, G. M.: *A Practical Treatise on Nervous Exhaustion (Neurasthenia): Its Symptoms, Nature, Sequences, Treatment*, New York, William Wood & Co., 1880.

The prevalence of neurocirculatory asthenia was high in mothers, fathers and siblings of patients.<sup>37</sup> The differences shown in table 6 between relatives of healthy controls and those patients with neurocirculatory asthenia are statistically significant. Figure 3 illustrates the familial pattern in the families of 15 of these patients as contrasted with the families of 15 healthy control subjects.

Since interviews with our patients suggested a possible familial prevalence, direct examination of 15 relatives was made. Results of the examinations corroborated the diagnosis in every case. This validated in part the method of diagnosing the condition from the history of relatives whom we did not examine.

Data on the familial incidence of other disorders show that manic-depressive psychosis, schizophrenia, angina pectoris and epilepsy are

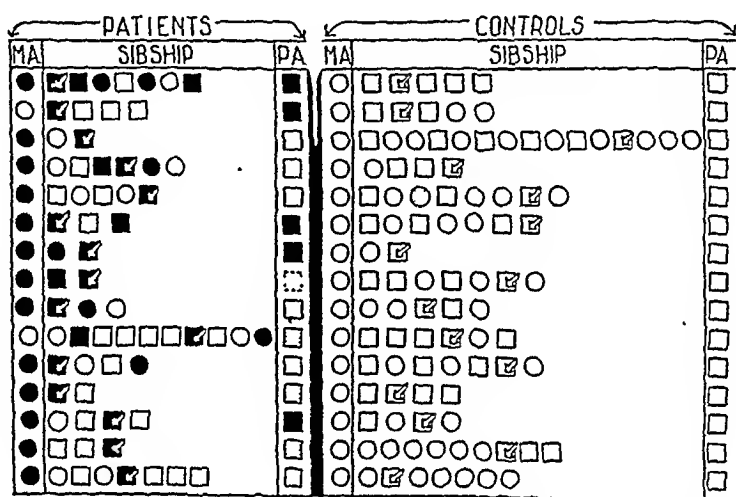


Fig. 3.—Familial incidence of neurocirculatory asthenia.<sup>1a</sup> This illustrates the familial pattern of the disorder in the families of patients as compared with the families of 15 healthy controls. The circle indicates females, the square males, the stippled square probable neurocirculatory asthenia, the black square neurocirculatory asthenia and the square with the arrow our patient or subject.

no more frequent among the close relatives of patients with neurocirculatory asthenia than they are among the close relatives of control subjects, which suggests that something more than the familial incidence of nonspecific neurologic, psychiatric or cardiologic disease is being dealt with.<sup>1a</sup>

In acute neurocirculatory asthenia there is but slight evidence of familial prevalence as compared with that in the chronic disorder.

The incidence of neurocirculatory asthenia in the 37 sons and daughters taken from a group of 50 parents diagnosed as having neurocirculatory asthenia twenty years ago was 48.6 per cent. This differed significantly from the incidence of the disorder of 5.6 per cent in 234 controls, the significance ratio being 5:1. This demonstrated that the incidence of neurocirculatory asthenia or anxiety neu-



rosis in the sons and daughters of patients with that disorder was significantly higher than in the general population.<sup>40</sup>

The data on familial prevalence was examined in the light of present day knowledge of human heredity.<sup>41</sup> When families with one affected parent are compared with those with two affected parents, the incidence in the offspring is 37 per cent and 62 per cent respectively. If the disorder is inherited, these figures suggest the possibility that the inheritance is that of the mendelian dominant. However, some of our data are inconsistent with this hypothesis, particularly the relatively higher incidence among mothers as compared with fathers. It is obvious that demonstration of familial prevalence does not necessarily imply that a disorder is hereditary. For instance, it might be contagious or related to other household factors.

#### COURSE

In patients already ill with neurocirculatory asthenia, symptoms are seemingly provoked by a wide variety of stimuli ranging from effort and emotion-provoking situations to no obvious factor. This characteristic of the disorder has been emphasized by previous writers on the subject.<sup>2a, b</sup>

#### ANATOMIC CHANGES

We have no information on the changes, gross or microscopic, observed at autopsy on subjects with neurocirculatory asthenia, nor are there any postmortem studies adequately described in the literature.<sup>41a</sup>

#### CAUSE

The cause or causes of neurocirculatory asthenia are unknown. We have no crucial data in this study that reveal the cause, nor are there any convincing studies in the literature. However, certain points are evident. First, in the search for the cause of chronic neurocirculatory asthenia, factors other than the immediate ones must be considered. Secondly, there is a high familial prevalence of the disorder. This suggests that search should be made for household or hereditary factors. Finally, a clear differentiation has to be made between the problem of the cause and the problems of what makes symptoms worse or what provokes an exacerbation. This differentiation is not always clearly made in the loose thinking that is sometimes present in the fields of

40. Wheeler, E. O.; White, P. D.; Reed, E., and Cohen, M. E.: Familial Incidence of Neurocirculatory Asthenia ("Anxiety Neurosis," "Effort Syndrome"), J. Clin. Investigation, to be published.

41. Roberts, J. A. F.: An Introduction to Medical Genetics, London, Oxford University Press, 1940.

41a. Hartshome, H.: On Heart Disease in the Army, Am. J. M. Sc. 48: 89, 1864. Da Costa.<sup>2a</sup>

so-called psychodynamics and psychosomatic medicine. Finally, the measurable abnormalities in this disorder must be given due consideration in establishing the cause.

#### COURSE AND BIOGRAPHIC EVENTS IN PATIENTS

This section will comprise a brief presentation of facts relating to the duration of the disorder, patients' answers to the question of what makes symptoms worse," factors associated with the onset or with exacerbation of the disease according to patients' histories, "emotional trauma" and "external physical" hardships during service. A follow-up of the course of the illness subsequent to our examination will also be discussed.

*Duration.*—The average age at the onset of the disease in 68 patients with the chronic form was twenty-one years, and the disease had lasted from three months to twenty-eight years, with a mean of seven years. Thirty-three patients with the acute form had an average age of 25 years, and the disease had lasted from two months to nine years, with a mean of 1.8 years. We should like to remind the reader of the somewhat unorthodox usage in this paper of the terms "chronic" and "acute" as applied to the disorder. Duration of symptoms is not the basis for these definitions but rather the period of good health and of ability to do work.

*What Makes Symptoms Worse?*—Patients' symptoms were made worse, according to their statements, by muscular work, by any strong emotion-provoking situation, by thinking about something unpleasant and often by no obvious stimulus. We observed only 5 patients of 76 with the chronic form of the disorder <sup>1a</sup> in whom muscular effort was the sole precipitant, and the same small percentage described an emotion-provoking situation as the sole precipitant of symptoms.

*Factors Associated with the Onset of Exacerbations as Judged From the Patients' Biographies.*—According to patients' stories, the onset of exacerbation of the disorder sometimes corresponds approximately in time with one or another of a wide variety of factors. In order of frequency of incidence these included family troubles, various types of infectious disease, overwork in service, father's cruelty, alcoholism or other misbehavior, death or illness in the family and many others.

This type of data is not particularly final in interpreting the course of the disease. First, we did not have collateral evidence in most cases as to the reliability of the patients' stories; secondly, the exact time relationship between biographic events and the course of disorder was not satisfactorily established and, thirdly, there is no necessary or automatic causal relationship between the events and the disorder even if they have close temporal relationship.

*Emotional Trauma and External Physical Hardship During Exercise.*—A tabulation was made of several sources of emotional trauma and of external physical hardships in military service. This was done to determine whether patients experienced more personal difficulties than did controls. No significant differences were found in the incidence of domestic problems between patients and healthy controls. Practically all patients (99 per cent of those with the chronic disorder and 85 per cent of those with the acute form) blamed the army for their difficulties and over 50 per cent believed, as did half of the convalescent wounded soldiers, that they were unfit for further service and that no treatment would help. A high percentage of patients with the acute form of the disorder and of convalescent controls reported a harrowing experience in combat. It is not clear to what extent these various differences reflected or influenced the symptoms or were reflections of particular attitudes of the patients.<sup>41a</sup>

*Follow-up Studies.*—Follow-up letters were sent to patients and to control subjects to find out what course the disorder had taken up to two years after examination. Of 39 patients, 85 per cent had been discharged from service. Three per cent reported that they were well, 85 per cent had symptoms off and on and in only 20 per cent was there unchanged. Twenty-six healthy control subjects were all still in service, and in none had neurocirculatory asthenia developed. This inadequate study demonstrated that discharge from military service does not automatically and immediately cure the disorder. These findings are in agreement with a larger follow-up study after World War I.<sup>42</sup>

From data collected in a twenty to twenty-five year follow-up<sup>42a</sup> of 55 patients, it was found that 15 per cent became completely well, 85 per cent had symptoms off and on and in only 20 per cent was there moderate or severe disability. These patients had been treated by "simple reassurance" for the most part.

Only 5 per cent of the men had significant disability. Of 177 patients in this study, 62 per cent were women and 38 per cent men, suggesting the distribution of the disorder between men and women in the civilian population.

Additional information on 166 of 173 patients in the study gives approximately the same follow-up results as above, which suggests a relatively benign course for this disorder and further that various therapeutic claims must be judged against knowledge of the course of the disorder over many years.

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42. Grant, R. T.: Observations on the After-Histories of Men Suffering from the Effort Syndrome, *Heart* 12:121, 1945.

42a. Wheeler, E. O.; White, P. D.; Reed, E., and Cohen, M. E.: Follow-up and Familial Studies in Neurocirculatory Asthenia (Anxiety Neurosis, Effort Syndrome), *Proc. New England Heart Assn.*, 1947-1948.

## COMMENT

No attempt is made here to summarize the literature on neurocirculatory asthenia. In many instances our work corroborates or extends observations of other workers. Various periods in the development of the concept of the disorder can be summarized in the beliefs of some of the more important workers. Da Costa,<sup>2a</sup> in describing the disorder in patients in the Civil War, did not limit his description to cardiovascular-respiratory symptoms but included nervous and digestive symptoms as well in his classic description of "irritable heart." He emphasized fever, diarrhea, hard field service and marching as important in causing the disorder. Sir Thomas Lewis<sup>2b</sup> in World War I recognized that the disorder had existed in many of his patients before the war. He sought to avoid the "presumption" that there is a cardiac malady by use of the term "effort syndrome," referring to the occurrence without adequate provocation of "symptoms and signs that follow exercise" if no signs of disease are anywhere discovered. Wood<sup>2c</sup> in World War II emphasized the resemblance of the symptoms to fear and was impressed by the importance of environment and experience in causing the disorder.

Our particular emphasis has been on the physiologic abnormalities, on the high familial prevalence of the disorder and on the chronic and acute types. We have demonstrated that the disorder is not identical with the symptoms of either effort or fear.<sup>1</sup> We do not believe that environment and experiences have been demonstrated either by us or by others to be the major factors in causing the disorder.

We conclude that neurocirculatory asthenia actually exists and is not evidence of malingering or simply a mechanism aroused during the war for purposes of evading military service. The disorder is common in civilian as well as in military life. Among other factors, the various terms used to refer to it make difficult the problem of assessing its exact frequency.

With regard to the various terms used, we would state that no term is ideal. We do not propose a new term or set of terms, believing that new names should await discovery of the cause or causes of what is now known as neurocirculatory asthenia, effort syndrome or anxiety neurosis. It is particularly important that present terminology should not mislead the users of it. For instance, if the term "anxiety neurosis" is used, it is important to realize that whereas anxiousness is one symptom of this disorder there are many others and that whereas anxiousness may provoke symptoms so do other factors. The same type of criticism applies to the use of "effort syndrome." The term "psychoneurosis" implies, to many, "psychogenic disorders." This assumption is somewhat premature since crucial evidence as to what causes "psychoneurosis" has still to be presented. The same type of criticism applies to all the terms including the term "neurocirculatory asthenia" itself. We have retained

this term in our work for the same reason as the authors<sup>43</sup> who proposed it, namely, because it was "moderately descriptive and noncommittal."

Our patients were divided into two groups, those with chronic and those with acute disorder, on the basis of history alone. It was of interest, however, that when observations on various subjects were tabulated, scores made by patients with acute disease were nearer those of the control subjects than were the scores made by patients with chronic disease. Whether the former patients had a milder form of the same disorder or an entirely different one we do not know.

In the physiologic investigation, studies made with the patients at rest revealed few abnormalities. As the work stress was greater, the evidence of abnormality increased, the deviation from normal being most marked when the stress was maximal. It is possible that the same pattern of findings might be demonstrated by the experimental use of forms of stress other than muscular work, such as emotion-provoking stimuli or situations. However, we emphasized tests of muscular work in this investigation because of immediate practical relevance and because we were unable to devise relevant and quantitatively standardized emotion-provoking situations.

The interest in neurocirculatory asthenia during wars should be commented on, since the major work in this field was done then. It seems probable that the chronic type of the disorder at least is a common one featured by remissions and exacerbations. If the exacerbations are really provoked, as patients believe, by unaccustomed muscular work, emotion-provoking situations, exposure, infectious disease and the convalescent state, the circumstances of war provide almost experimental conditions for exacerbations. However, the exact importance of these various factors has as yet not been studied quantitatively or experimentally in previous wars or in this one. Neurocirculatory asthenia was common in this war too, although its true incidence was obscured by its many labels.

No specific effective cure has been developed. Our studies certainly do not add to this aspect. It is possible that specific therapy may be forced to await discovery of causal or fundamental mechanisms in the disorder. Evaluation of therapeutic claims must be based on knowledge of the clinical course of the disorder and on awareness of the fact that it is characterized by remissions as well as by exacerbations.<sup>43a</sup>

#### SUMMARY

The present paper summarizes the major positive findings in a five year study of neurocirculatory asthenia, effort syndrome or anxiety neurosis. In successive sections the following points are made:

43. Oppenheimer, B. S.; Levine, S. A.; Morison, R. A.; Rothschild, M. A.; St. Lawrence, W., and Wilson, F. N.: Report on Neurocirculatory Asthenia and Its Management, *Mil. Surgeon* 42:409, 1918.

43a. Cohen and others.<sup>1a</sup> Wheeler and others.<sup>42a</sup>

1. Terminology concerning this disorder is confused, with no satisfactory distinction between neurocirculatory asthenia, anxiety neurosis, effort syndrome, neurasthenia, psychoneurosis, combat fatigue and other terms.

2. Symptoms are multiple and high in incidence. In contrast, physical signs are few.

3. Studies of muscular work demonstrate short duration of performance in hard work and a defect in aerobic metabolism in all grades of work as evidenced by oxygen consumption and blood lactate concentration. Pulmonary ventilation is abnormal during work, as is ventilatory efficiency.

4. Ventilation index and awareness of dyspnea are abnormal.

5. The pulse rate for all grades of exercise is abnormally high. The capillaries of finger nail folds are abnormal. The size of the heart, the electrocardiograms and the resting circulatory measurements, including cardiac output, are normal.

6. Quantitative studies of pain and discomfort show abnormal reaction to painful stimuli.

7. Psychologic tests place patients with neurocirculatory asthenia in the "neurosis" category.

8. The incidence of neurocirculatory asthenia is high in mothers, fathers, brothers and sisters of patients with the disorder. If the disorder is hereditary, the data suggest mendelian dominance.

9. The cause, anatomic changes and specific treatment are obscure.

10. The symptoms, onset and exacerbations are influenced, according to patients' biographic reports, by muscular work, emotion-provoking situations, infection or nothing at all. The difficulties in interpreting this type of data are emphasized.

11. A convenient distinction was made on the basis of history alone between acute and chronic neurocirculatory asthenia. In this study "acute" refers to the disease in patients with a convincing history of previous health and ability to do hard work. "Chronic" refers to the disease in patients who had never been able to do hard work or athletics.

12. In all studies in which differences existed between patients and healthy controls mean values for those with the acute form of the disease fell between those for controls and those for patients with the chronic form.

13. It is emphasized in studies of this disorder, and perhaps in many others, that basal measurements made with the patients resting may not show abnormalities while measurements made while the patients are under stress may; the stronger the stress the greater the deviation from normal.

# EFFECT OF LANATOSIDE C ON THE CIRCULATION OF PATIENTS WITH CONGESTIVE FAILURE

A Study Using Catheterization of the Right Side of the Heart

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THE METHOD of catheterization of the right side of the heart has made it practical to measure the cardiac output by the Fick principle in patients acutely ill with congestive failure. The purification of digitalis glucosides has made it safe to give a therapeutically effective dose of digitalis in a single intravenous injection. It is now possible in a few hours to make observations on the circulation before and after the drug has had its effect. Such observations are much easier to interpret than those made at intervals of one day or longer. The purpose of this paper is to report the data on changes in circulation produced by the intravenous administration of 1.6 mg. of lanatoside C in 22 patients with congestive heart failure.

## METHOD

The patients were studied either immediately after their admission to the hospital or on the following morning. Food was withheld for twelve hours before the observations if the patient was in the hospital. Those studied on entry to the hospital had been too ill to eat much food on the day of admission. Patients received morphine if dyspnea was severe, and many of them were supported by a back rest which raised the trunk to an angle of about 30 degrees.

The right side of the heart was catheterized by the method previously described.<sup>1</sup> In most instances the sample of mixed venous blood was obtained from the

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1. Berconsky, I.: El volumen circulatorio per minute en el estado normal y patologico, *Semana méd.* 2:570, 1930. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, *Proc. Soc. Exper. Biol. & Med.* 46:462, 1941. Warren, J. V.; Stead, E. A., Jr., and Brannon, E. S.: The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization, *Am. J. Physiol.* 145:458, 1946.

right auricle; in a few it was obtained from the right ventricle. Mixing may well be less complete in dilated hearts than in those of normal subjects. This problem was not investigated. Samples of arterial blood were obtained from the femoral artery. The oxygen content of the arterial and venous blood was measured by the method of Van Slyke.<sup>2</sup> The oxygen consumption was calculated from analysis of samples of expired air by the method of Haldene.<sup>2</sup> The cardiac output was calculated according to the Fick principle and recorded as liters per minute. The difficulty in computing surface areas in patients with varying degrees of edema makes the calculation of the cardiac index of less value.

The arterial pressure was recorded from the femoral artery by the method of Hamilton.<sup>3</sup> The mean atrial pressure was measured with a saline manometer, a point 5 cm. below the fourth costochondral junction being taken as a reference point. The peripheral resistance was recorded in absolute units and calculated from the formula:

$$R = \frac{P_m (\text{mean pressure in mm. of Hg.}) \times 1,332}{CO (\text{cardiac output in cc. per second})}$$

Heparin was used as the anticoagulant for hematocrit readings.

None of the patients had received digitalis in the preceding three weeks. After the control observations were made, 1.6 mg. of lanatoside C was injected intravenously. There were no untoward reactions.

## RESULTS

All patients had had dyspnea on slight exertion and had had orthopnea before sedation. Peripheral edema was present in varying degrees, and the right atrial pressure was elevated in 21. Auricular fibrillation was present in 3 patients and paroxysmal auricular tachycardia in 2. The remainder had normal sinus rhythm. Patients with frank Cheyne-Stokes breathing were excluded from this series. In many, however, breathing was somewhat irregular and the values for oxygen consumption were less accurate than in normal subjects.

Thirteen patients had hypertension or coronary artery disease, 4 had rheumatic heart disease with mitral stenosis, 3 had syphilitic heart disease with aortic insufficiency and 2 had unclassified heart disease (1 with marked pulsus alterans and the other with auricular tachycardia).

The first observed effect was a fall in venous pressure, which began in five to ten minutes and continued for thirty to sixty minutes. The smallest fall was 20 mm. of water and the largest 135 mm., the average being 62 mm. The decrease in venous pressure was not preceded by diuresis and seemed to be independent of a decrease in

2. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

3. Hamilton, W. F.; Brewer, G., and Brotman, I.: *Pressure Pulse Contours in the Intact Animal: I. Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures*, *Am. J. Physiol.* 107:427, 1934.



blood volume.\* These observations are similar to those recorded by La Due.<sup>4</sup> The hematocrit reading fell during the period of observation in 14, remained unchanged in 6 and increased in 1. The fall in hematocrit reading may be the result of hemodilution caused by the fall in venous pressure. The total amount of blood drawn for measuring the cardiac output was not carefully determined, and it is possible that the fall was the result of repeated sampling.

The response of the cardiac rate was variable. In 6 patients the rate increased, in 2 it remained unchanged and in 14 it decreased. However, the stroke volume nearly always improved, being increased in 20 and lowered in only 2. There was no consistent change in oxygen consumption. The mean arterial pressure usually increased; it showed a rise of from 1 to 50 millimeters of mercury in 16 of the 20 patients in whom it was measured. The systolic pressure rose in the 20 patients in whom the measurement was made, the rise ranging from 4 to 50 millimeters of mercury. There was no consistent change in diastolic pressure. The peripheral resistance fell in eighteen of twenty observations.

The arteriovenous oxygen difference decreased in all but 1 instance. In 4 instances the decrease was 0.3 volumes per cent or less. These differences are not significant. In 16 the fall was 0.9 volumes per cent or greater. In 2 patients with marked anemia the fall was 0.5 volumes per cent, which is probably significant. Thus 18 of 22 had a significant narrowing of the arteriovenous oxygen difference. The cardiac index rose in twenty of the twenty-two observations. If the patients in whom the change in arteriovenous oxygen difference was not significant were eliminated, the increase in cardiac output would average 1.6 liters per minute, with a range of from 0.2 to 4.2 liters per minute.

#### COMMENT

The data are surprisingly consistent. In patients with congestive failure lanatoside C produced a rise in cardiac output, an increase in stroke volume, a rise in systolic and mean arterial pressure and a fall in atrial pressure and in peripheral resistance. The determination of the cardiac output is based on the arteriovenous oxygen difference and on the quantity of oxygen removed from the lungs per minute. For this group of severely ill patients the determination of oxygen consumption was less reliable than the measurement of the arteriovenous oxygen difference. Therefore digitalis was not considered to have had a significant effect on the cardiac output in instances in which the arteriovenous difference did not show a significant decrease. The

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4. La Due, J. S., and Fahr, G.: Effect of Intravenous Administration of Lanatoside C upon Output, Diastolic Volume, and Mechanical Efficiency of Failing Human Heart, *Am. Heart J.* 25:344, 1943.

average increase in cardiac output in the 18 patients in whom the drug caused a fall in arteriovenous oxygen difference was 1.6 liters per minute. This was an increase in output of 2,300 liters, or 575 gallons, per twenty-four hours. It is no wonder that Withering was impressed by digitalis.

The increase in cardiac output occurred in patients with normal rhythm, paroxysmal auricular tachycardia and auricular fibrillation. The data support the thesis that digitalis has a direct effect on the strength of contraction of the ventricles and that its effect is not dependent on a reduction in cardiac rate.

The increase in cardiac output was accompanied with a rise in mean and systolic arterial pressures. This rise was not as great as it would have been if the peripheral vessels had not dilated. The data indicate that the fall in peripheral resistance was not sufficient to offset completely the effect on arterial pressure of a rise in cardiac output.

This study is of particular interest because of the information which it gives on the relation between the cardiac output and the development of congestive failure. In 3 patients (A. M., C. H. and T. W.) the cardiac output as related to surface area was increased in the presence of congestive failure. These patients were anemic, and the cardiac output even in the absence of failure would have been greatly increased.<sup>5</sup> When the heart began to fail the output dropped below the level needed by the body and the signs and symptoms of congestive failure developed. That this interpretation is correct and that the body was receiving too little blood even though the output was above the expected basal level is shown by the fact that in each patient the output was increased by the administration of lanatoside C. In 4 patients (D. W., K. Mc., C. Mc. and R. N.) the arteriovenous oxygen difference and the cardiac outputs as related to surface area were within the extremes of the normal range. Was the cardiac output adequate for the tissue needs? The finding of an increase with lanatoside C suggests that the output was not optimum for the needs of the body. Similar observations have been reported in regard to persons with pericardial tamponade. The cardiac output in certain instances of purulent pericarditis may be greatly increased. The fact that it is causing an inadequate circulation becomes obvious when the tamponade is relieved and the output climbs to still higher levels.<sup>6</sup>

5. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technique of Right Atrial Catheterization, *J. Clin. Investigation* **24**:332, 1945.

6. Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: Pericardial Tamponade from Stab Wound of the Heart and Pericardial Effusion or Empyema: A Study Utilizing the Method of Right Heart Catheterization, *Am. Heart J.* **31**:418, 1946.

*Effect of the Intravenous Injection of 1.6 Milligrams of Lanatoside C*

Subject	Age	Sex	Sur- face Sq. M.	Oxygen Con- sump- tion, Cc. per Minute	Arterial Satura- tion, %	Oxygen Content, Vol. %		Arterio- venous Differ- ence, Vol. %	Car- diac Out- put, Liters per Min.	Stroke Vol- ume, Cc.	Heart Rate	Arterial Pressure, Mm. Hg		Periph- eral Resis- tance, Units	Atrial Pres- sure, Cc. of H <sub>2</sub> O	Hema- to- crit Rend- ing
						Arte- rial	Mixed Venous					Sys- tole	Diast- tole			
A. M. W.	39	F	1.38	138	..	6.3	3.2	3.1	6.1	59	104	223	108	1,870	225	16
				148	..	6.0	3.5	2.5	8.2	85	96	237	96	1,450	170	16
O. B. H.	33	F	1.74	163	..	7.2	4.1	3.1	9.2	92	100	266	133	1,610	125	19
				163	..	7.2	4.6	2.6	11.0	81	136	...	...	.....	15	17
C. P.	43	F	1.80	113	94	14.7	6.0	8.7	2.3	13	178	102	82	2,890	185	38
				119	96	14.0	10.7	3.3	6.5	92	71	150	80	1,290	50	35
				108	94	14.9	10.2	4.7	4.1	63	60	144	74	1,850	25	37
				214	..	13.5	7.0	6.5	5.8	39	150	159	110	1,700	75	32
D. W.	74	M	1.70	214	..	13.4	8.1	5.3	7.1	80	84	164	97	1,310	5	32
				214	..	13.4	8.1	5.3	7.1	80	84	164	97	1,310	5	32
T. S.	54	M	1.85	123	91	14.4	6.5	7.9	2.9	21	120	108	80	2,390	215	38
				120	91	11.7	6.9	4.8	4.6	63	68	128	75	1,470	165	35
				142	94	14.6	9.7	4.9	4.9	64	76	133	72	1,440	65	35
				171	..	14.6	9.7	4.9	4.9	64	76	133	72	1,440	65	35
H. T.	73	M	1.57	139	83	15.4	8.3	7.1	3.1	31	100	139	87	2,910	250	45
				135	83	15.3	8.5	6.8	3.1	27	116	157	99	3,590	230	45
K. Me.	49	F	1.94	155	..	18.8	13.4	5.4	5.6	75	75	198	96	1,760	113	52
				163	..	19.4	15.6	3.8	8.3	105	79	206	108	1,320	70	55
H. S.	40	M	1.70	139	..	14.1	6.5	7.6	3.1	33	94	212	51	2,500	245	40
				167	..	14.1	7.6	6.5	4.4	47	94	237	56	1,910	190	39
J. H.	42	M	1.92	182	..	16.6	5.8	10.8	3.2	38	84	202	73	2,800	150	44
				137	..	14.8	7.0	7.8	3.4	47	72	226	67	1,700	145	40

H. H.	Syphilitic aortic insufficiency, 50 minutes after lanatoside O..	46	M	2.0	225	204	..	16.7	6.1	10.6	4.2	42	100	205	86	151	2,810	160	48
R. A. W.	Hypertensive heart disease, 50 minutes after lanatoside O..	49	M	1.90	126	122	..	14.9	7.6	7.3	3.3	32	104	147	102	114	2,760	120	39
L. H.	Hypertensive heart disease, anemia, uremia ..... 70 minutes after lanatoside O..	40	F	1.58	108	113	..	8.5	4.0	4.5	3.8	43	88	227	128	162	3,430	210	20
F. M.	Hypertensive heart disease, 1 hour after lanatoside O.....	51	M	1.96	173	169	81	13.9	6.5	8.4	4.0	47	86	208	133	155	3,080	250	41
C. Me.	Hypertensive heart disease, 70 minutes after lanatoside O..	63	M	1.82	166	182	..	15.2	9.0	6.2	4.9	52	94	200	130	162	2,470	135	42
T. W.	Hypertensive heart disease, anemia, uremia ..... 60 minutes after lanatoside O..	35	M	1.67	150	149	96	5.2	3.0	2.2	11.4	130	88	150	100	125	880	300	14.4
J. G.	Rheumatic heart disease, mitral stenosis ..... 60 minutes after lanatoside O.. 3 weeks later.....	30	M	1.75	121	137	92	15.0	5.4	9.6	2.2	18	124	137	97	105	3,780	215	43
L. H.	Rheumatic heart disease, mitral stenosis ..... 60 minutes after lanatoside O.. 24 days later.....	41	M	1.91	149	169	70	13.7	7.3	6.4	4.4	43	104	116	72	80	1,460	195	42
N. J.	Rheumatic heart disease, mitral stenosis ..... 90 minutes after lanatoside O..	39	F	2.22	176	108	..	12.5	4.5	8.0	4.9	44	112	195	88	126	2,060	300	38
R. N.	Myocardial infarction ..... 60 minutes after lanatoside O..	40	F	1.67	153	166	..	10.3	6.0	4.8	5.3	47	112	64	44	50	750	150	34
A. P.	Etiology unknown ..... 60 minutes after lanatoside O.. 13 days later.....	40	M	1.90	109	114	85	14.4	6.4	8.0	2.6	25	104	89	66	69	2,140	290	42
E. M.	Coronary arterial disease..... 75 minutes after lanatoside O..	33	M	1.96	153	153	..	15.1	7.3	7.3	4.1	37	111	158	97	119	2,330	270	46
A. W.	Coronary arterial disease..... 60 minutes after lanatoside O..	58	M	2.1	145	143	90	17.2	7.7	9.5	3.2	28	112	137	100	108	2,710	220	47
								16.4	8.5	7.9	3.8	35	108	140	100	108	2,280	170	45

These observations stress again the fact that the adequacy of the output of the heart must be determined in relation to the needs of the body for blood. If the need is low, as in myxedema,<sup>7</sup> a considerable reduction in cardiac output may occur without the development of the signs and symptoms of congestive failure. If the needs of the body are great, as in exercise<sup>8</sup> or hyperthyroidism, congestive failure may occur with a high output. When the heart is unable to pump sufficient blood to supply all the tissues, the renal blood flow is sharply reduced, the filtration rate falls and sodium retention occurs. This sequence of events may occur with any absolute value for cardiac output.

The fall in venous pressure could not be correlated with the magnitude of the increase in cardiac output. In certain patients the venous pressure fell to normal levels within one hour. In others the pressure fell during the first hour but leveled off at an abnormally high value and did not fall to normal during the period of observation. It has been pointed out that the venous pressure is greatly influenced by two factors in cardiac failure: (1) the tone of the vascular bed and (2) the blood volume.<sup>9</sup> In chronic heart failure both the blood volume and the tone of the vascular system are increased. There is considerable vasoconstriction in the kidneys, the peripheral resistance is raised and the venous pressure is increased. The first two of these changes occur in reversible shock from hemorrhage. The third is absent because even intense vasoconstriction cannot raise the venous pressure if the blood volume is greatly decreased. The vascular constriction in heart failure and in acute hemorrhage probably results from the fact that in both the cardiac output is reduced. Whether the constriction is humoral or reflex or both has not been determined. Digitalis, when effective in improving the circulation, reduces the tone in the vascular bed. The blood flow to the kidneys increases, the peripheral resistance falls and the venous pressure drops. Whether these changes in vascular tone occur because of the improvement in cardiac output alone or whether they are in part the result of a peripheral action of lanatoside C itself has not been determined. The primary fall in atrial pressure appears to be related to the changes in venous tone just described. The further fall in venous pressure which may occur during the next few days appears to be related to the decrease in blood volume caused by the diuresis.

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7. Unpublished data.

8. Hickam, J. B., and Cargill, W. H.: *Effect of Exercise on Cardiac Output and Pulmonary Arterial Pressure in Normal Persons and in Patients with Cardiovascular Disease and Pulmonary Emphysema*, to be published.

9. Warren, J. V., and Stead, E. A., Jr.: *Fluid Dynamics in Chronic Congestive Heart Failure*, *Arch. Int. Med.* **73**:138 (Feb.) 1944.

McMichael and Sharpey-Schafer<sup>10</sup> have called attention to the fact that lowering of the venous pressure by pooling of blood in the extremities will cause an increase in cardiac output in certain persons with congestive heart failure. They have emphasized the fall in venous pressure produced by intravenous administration of digoxin and have suggested that the major benefits of digoxin treatment result from a peripheral action on venous pressure. Other authors,<sup>11</sup> reporting on the effects of ouabain, have found no correlation between the effect on venous pressure and the rise in cardiac output. The data reported here likewise show no relationship between the magnitude of the fall of venous pressure and the degree of increase in cardiac output. Observations on the effects of venesection from this laboratory indicate that in patients with congestive failure a fall in venous pressure may be accompanied with a rise in cardiac output.<sup>7</sup> Recent observations by Hickam and Cargill<sup>8</sup> on the effects of exercise on the cardiac output of patients with congestive failure are helpful in the interpretation of these findings. During exercise the cardiac output in patients with severe congestive failure may fall below the resting level. The heart in these patients is inadequate at rest. When pushed harder it becomes even less adequate. When the exercise stops the cardiac output presumably returns eventually to the resting level, though studies were not made after exercise. These observations indicate that in the presence of heart failure any procedure that normally decreases the work of the heart may instead result in an actual increase in output. Lowering the venous pressure by venesection tends to reduce pulmonary congestion, diminish reflex activity and in certain instances lower the arterial pressure. These effects may well reduce the requirements of the body for blood. In severe carditis decreasing the work required of the heart by venesection may well cause a rise, rather than a fall, in cardiac output.

The data recorded here on the effect of lanatoside C on the circulation are much more consistent than those recorded on the use of the slower-acting oral preparations of digitalis. This was to be expected because, as previously pointed out, the output of the heart at rest may rise, fall or remain unchanged over a period of several days while the patient is compensating.

The cardiac output in congestive failure may be classified as follows:

1. The output is low on the patient's admission to the hospital, and it remains low. Compensation results entirely from the use of salt

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10. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Intravenous Digoxin in Man, *Quart. J. Med.* **13**:123, 1944.

11. Bloomfield, R. A.; Rapoport, B.; Milnor, J. P.; Long, W. K.; Mebane, J. G., and Ellis, L. B.: The Effect of Ouabain on the Dynamics of the Circulation in Patients with Congestive Heart Failure, *J. Clin. Investigation*, to be published.

restriction and mercurial diuretics. Edema will develop if the patient is placed on a normal diet.

2. The output is low on the patient's admission to the hospital, and it increases on digitalization. Compensation occurs without the use of salt restriction or diuretics.

3. The output is normal on the patient's admission to the hospital, and it remains normal while he is confined to bed. It is adequate for the resting state but inadequate in the presence of activity or infection. The symptoms on admission to the hospital result from waterlogging and congestion in the lungs which occurred during activity or were precipitated by an infection. Reduction of activity or clearing of infection allows adequate output at rest. Signs and symptoms disappear as long as activity is sharply restricted.

4. The output is high on the patient's admission to the hospital, and it falls with compensation. The output is increased over the normal resting level because of anxiety, discomfort or some associated disturbance such as anemia, beriberi or arteriovenous fistula. It is higher than the normal basal level but not high enough to meet the needs of the body. If the demands of the body for blood are lowered, the resting cardiac output decreases as compensation occurs.

It is clear that the results from rapid and slow digitalization would cause no confusion in groups 1, 2 and 3. No patients in the series reported here fell in group 3. The findings in group 4 will differ by the two methods. If a restless, apprehensive patient with moderate failure is studied, the output on his admission to the hospital may be high. If digitalization is rapidly carried out, the fact that the output is still not high enough for the state of the patient will become obvious as the output rises to a still higher level with digitalization. Since the output is now adequate for the needs of the patient, the signs and symptoms of congestive failure will disappear. The patient loses his restlessness and apprehension, and the requirement of the body for blood decreases. The cardiac output therefore falls. The higher output on his admission to the hospital was inadequate for body needs; the lower output is now adequate, and the signs and symptoms of congestive failure do not recur.

The initial rise in output produced by digitalization may be completely overlooked unless observations are made within a short time after the effect of digitalis has occurred. Similar results are seen in patients with congestive failure and severe anemia. The output is high but not high enough for the body needs, and failure occurs. Digitalization causes a further rise in output. When the anemia is corrected, the cardiac output falls below the level present before digitalization.

## SUMMARY AND CONCLUSIONS

1. The effect of the intravenous injection of 1.6 mg. of lanatoside C on the circulation in 22 patients with congestive heart failure was observed. The right side of the heart was catheterized in order to obtain samples of mixed venous blood and to measure the right atrial pressure.

2. The first measurable effect of lanatoside C was on the atrial pressure. The average fall during the first sixty to one hundred and twenty minutes was 62 mm. of water.

3. In 18 of the 22 subjects the cardiac output increased significantly. The average increase was 1.6 liters per minute. This represents an increase in blood flow to the tissues of 2,300 liters per day.

4. There was no consistent change in oxygen consumption. The increase in output resulted primarily from a decrease in arteriovenous oxygen difference.

5. The systolic and mean arterial pressures rose and the peripheral resistance fell.

6. The response of the cardiac rate was variable, but in 20 of the patients the stroke volume increased.

7. Patients with severe anemia and congestive heart failure may have a high cardiac output. Digitalis may cause a still further increase in output.

8. Certain patients with congestive heart failure have an insufficient cardiac output though the cardiac index and the arteriovenous oxygen difference are within the extreme limits of normal. That the output is inadequate is suggested by the increase which occurs with digitalization.

9. The data indicate that lanatoside C increases the output of the heart in the presence of a normal rhythm and that the prime action of digitalis is on the ventricular muscle, which enables the ventricles to increase their output.



## PLACE OF INTERMITTENT VENOUS HYPEREMIA IN THE TREATMENT OF OBLITERATIVE VASCULAR DISEASE

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**I**N A PREVIOUS communication, Hick, Coulter and one of us<sup>1</sup> summarized the reasons which prompted the use of intermittent venous hyperemia in cases of obliterative vascular disease. At that time (1937) the number of patients who had used this treatment was small, and they had not used the method originally advocated by Collens and Wilensky<sup>2</sup> for a long time. The conclusions were tentative.

The rationale of this treatment has remained controversial, and there are still a number of vascular clinics in which its efficacy is doubted.<sup>3</sup> Others employ it when the extremity is obviously lost and waste valuable time or hasten the absorption of toxins from gangrenous toes.

The purpose of this communication is to present our indications for this form of treatment and the results obtained from it. This report is based on 100 consecutive unselected cases taken from the office files, and it excludes all patients who have had other types of treatment, especially sympathectomy, although, as will be pointed out, the method is routinely used after sympathectomy for occlusive vascular disease, after embolectomy and after amputation of one limb for the protection of the other.

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1. de Takats, G.; Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in Treatment of Peripheral Vascular Disease, *J. A. M. A.* **108**:1951 (June 5) 1937.

2. Collens, W. S., and Wilensky, N. D.: The Use of Intermittent Compression in the Treatment of Peripheral Vascular Disease, *Am. Heart J.* **11**:705, 1936.

3. Allen, E. V., and McKechnie, R. D.: Effect of Intermittent Venous Occlusion on the Circulation of the Extremities, *J. Lab. & Clin. Med.* **22**:1260, 1937. Veal, J. R., and McLord, W. M.: Blood Oxygen Changes Following Intermittent Venous Occlusion, *Am. Heart J.* **17**:401, 1939. Harpuder, K., and Stein, I. D.: Therapeutic Value of Passive Hyperemia in Peripheral Vascular Disease, *Arch. Phys. Therapy* **20**:9, 1939. Abramson, D. I.; Zozeela, H., and Schkloven, N.: The Vasodilating Action of Various Therapeutic Procedures Which Are Used in the Treatment of Peripheral Vascular Disease: A Plethysmographic Study, *Am. Heart J.* **21**:756; 1941.

## METHODS OF STUDY

The grade of obliterative vascular disease is always determined before treatment is instituted. In a previous communication, Beck, Roth and one of us<sup>4</sup> emphasized the point that all therapeutic methods tested should be correlated with the stage of the occlusive vascular disease during which they are undertaken. This is true of intermittent venous hyperemia as it is of sympathectomy.<sup>5</sup> The four stages may be summarized as follows:

Grade 1. The patients have diminished or absent pulsations of the foot or the lower part of the leg. The skin is warm, and the color of the feet is normal. They can walk a distance of two to six blocks without pain.

Grade 2. The feet of the patients in this stage are pulseless, and they are unable to walk a distance of two blocks without pain. However, trophic changes may still be absent although the feet are cold and dry, and a single toe is often cyanotic. A cold and moist foot, incidentally, always indicates a better prognosis because the patients exhibit a heightened sympathetic tone, the release of which warms up their skin.

Grade 3. Pain at rest and intractable ischemic neuritis are present at this stage. Walking may be less painful, or it may even offer relief when rest in bed is difficult. When the foot is ice cold and when arteriolar obstruction and capillary paralysis are obvious from the pronounced dependent rubor, sympathectomy is of no use and may precipitate gangrene.

Grade 4. The patients exhibit ulceration and gangrene of the digits or of parts of the foot. The lesion is dry and not too painful. There is no evidence of infection. The popliteal pulse is absent, and possibly the femoral pulse is also absent. Supracondylar amputation at the level of positive histamine flares used to be the surgical procedure of choice for these patients. However, a sympathetic block may so shift the level of circulatory efficiency that amputation of the lower part of the leg or a midmetatarsal amputation can be tolerated.

Next, the amount and duration of constriction is determined by inflating a blood pressure cuff at the mid-thigh to a subdiastolic pressure, usually 60 mm. of mercury, and maintaining this pressure until a maximal distention of the dorsal veins and a satisfactory rubor of the toes appear. Obviously the more severe the vascular lesion, the longer it will take for the capillaries to dilate and for the veins to fill. If more than four minutes are required for this purpose, the patient must have a severe arterial and arteriolar obstruction, and the fate of the limb is doubtful. In patients with visible signs of venous stasis, cyanosis of toes, the pressure should not exceed 40 mm. of mercury, and the cuff should not be kept on longer than is necessary to produce a rubor. The duration of the release of pressure should be as long as it takes for the foot (or hand) to take on the color and the venous filling which it exhibited prior to constriction. In our experience, this never takes longer than one minute, but a slight elevation of the treated extremities on a pillow facilitates the drainage of trapped blood. Heating the abdomen with a cradle helps to diminish the vasomotor tonus in the extremity.

4. de Takats, G.; Beck, W. C., and Roth, E. A.: The Neurocirculatory Clinic: A Summary of Its Activities, *Ann. Int. Med.* **13**:957, 1939.

5. de Takats, G.; Risley, T. C.; Jordan, P., and Fowler, E. F.: Sympathectomy in the Treatment of Peripheral Vascular Sclerosis, *J. A. M. A.* **131**:495 (June 8) 1946.

The factors observed before the constrictor is prescribed are as follows: rate of pulse, color of feet, the drop in the temperature of the skin, venous filling time, oscillometric curves, walking ability and the rise in the temperature of the skin after sympathetic block. General cardiovascular tests, including determinations of the blood sugar, blood cholesterol and nonprotein nitrogen contents and electrocardiographic and concentration-dilution tests, are always included. Of these tests, a few need further comment. Walking ability is determined by having the patient walk on level ground (in a corridor) at a rate of ten paces in ten seconds until the muscles of the calf begin to ache or the toes become numb. It is perfectly clear that this ability varies a great deal in the same patient from day to day, depending on the temperature of the room, on the ground he is walking on (whether cement or grass) and on premedication. Acetylsalicylic acid, pentobarbital sodium and narcotics will prolong the period before claudication develops. Nevertheless it is still the simplest and most useful of all tests and one that the patient can report on later when returning for follow-up examinations.

The venous filling time described by Collens and Wilensky<sup>6</sup> has been modified as follows. The limb to be examined is elevated to empty the superficial veins on the dorsum of the foot and to relieve it of any cyanosis or rubor. A blood pressure cuff is placed on the thigh of the patient and inflated to 60 mm. of mercury while the leg is still elevated. The leg is then put in the horizontal position, and the foot is placed under adequate natural or artificial light. The time of venous compression is noted and also the time it takes for the dorsal veins to be raised from the skin level, after which they may show venous pulsation. This end point is not always easy to read; for normal healthy persons, not more than five to ten seconds are sufficient to produce venous stasis, and for patients with severe arterial obliteration, two to six minutes may elapse before adequate venous filling is observed. The test is made at room temperature, and the comparative values from the two sides are especially significant. This is really a rough circulation time and perhaps is the best clinical test for any detectable improvement after treatment with intermittent venous hyperemia. The duration of stasis is always much shorter than the duration of constriction, since during the latter a stretching of the venocapillary bed is the object.<sup>1</sup>

Temperatures of the skin are determined with a small portable electric thermometer, again at room temperature, before and after sympathetic block. A good rise in the temperature and a markedly increased walking ability speak for the advisability of sympathectomy if other parts of the cardiovascular apparatus are not notably involved. When there is a poor response to sympathetic block or if there is marked coronary, cerebral or renal involvement, the constrictor substitutes for sympathectomy. Thus, the data reported here deal with patients in advanced stages of the disease.

#### INDICATIONS FOR THE USE OF INTERMITTENT VENOUS HYPEREMIA

1. Intermittent venous hyperemia is indicated after acute arterial occlusion if embolectomy or sympathectomy is not feasible or after any one of these operations as postoperative treatment. If venous thrombosis is present, the treatment may increase edema or facilitate embolization. However, in many hundreds of cases we have not actually seen

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6. Collens, W. S., and Wilensky, N. D.: Two Quantitative Tests of Peripheral Vascular Obstruction, *Am. J. Surg.* **34**:71, 1936.

this happen. In cases of minor emboli, sympathetic block combined with the use of a rhythmic constrictor may make an embolectomy unnecessary, but if the patient is seen within the first ten hours embolectomy is always preferable. For acute thromboses, sympathetic block combined with venous hyperemia and the use of papaverine for the relief of pain and heparin to prevent spreading of thrombosis constitute our choice of methods.<sup>7</sup> When a sudden thrombosis, with peripheral embolization, has taken place in sclerotic patients with popliteal aneurysms, sympathectomy and intermittent venous hyperemia should precede the obliteration of the sac; at least a six week treatment is advisable before a direct attack on the aneurysm is undertaken.

2. Intermittent venous hyperemia is indicated for patients with chronic arterial occlusions due to arteriosclerosis with and without diabetes, to syphilis or to thromboangiitis obliterans. Many of these patients do well if they are subjected to sympathectomy, particularly if the operation is carried out in the early stages. Patients with thromboangiitis obliterans, unless they are in the late "burned out" stage, exhibit considerable vasospasm, and, as pointed out in our first communication,<sup>1</sup> intermittent venous compression may aggravate such spasm. Therefore, all patients with obliterative vascular disease exhibiting vasospasm first are subjected to sympathectomy before the described treatment is begun. In cases of ischemic and diabetic neuropathy, venous hyperemia seems to be of no avail; in fact, it often aggravates the pain.

#### CONTRAINDICATIONS

From what has been said in the foregoing paragraphs, it is obvious that we advise against the use of the apparatus (1) in acute venous thrombosis, (2) in lymphangitis, (3) in severe arteriolar obstruction and (4) in the presence of frank gangrene. In addition, the treatment has been found useless for neuropathies, whether ischemic or metabolic, causalgic states, sequelae of frost bite, trench foot or immersion limb. To establish such treatment when other methods are available or necessary seems a grave error.

#### RESULTS OF TREATMENT

For the clinical evaluation of this treatment, we have selected 100 cases in which no other form of treatment was employed. Even in such cases, as Silbert has pointed out,<sup>8</sup> there is a natural course of

7. de Takats, G.: Surgical Treatment of Acute Vascular Occlusions, *S. Clin. North America* 22:199, 1942.

8. Silbert, S.: Evaluation of Results in Treatment of Peripheral Circulatory Disease, *Am. Heart J.* 15:255, 1938.

slow improvement unless some acute vascular accident is superimposed on the chronic arterial insufficiency. Nevertheless, our records indicate an unmistakable benefit to be derived by the properly selected patient. After the preliminary tests, the patients are instructed to rent or buy an automatic apparatus, use it at home for two or three hours daily and then report every three months for the first year, twice a year for the second year and once the third year. Our data have been collected on the basis of these observations; the patients stay at work and use the equipment in the morning and in the evening or at night.

Of the 100 patients, 15 were women and 85 were men. Table 1 summarizes the results, which are grouped according to four grades. We noted in our records that subjective improvement was registered in a higher percentage than objective improvement. This may be due to autosuggestion, but in a few carefully studied cases it was simply because of the fact that the tests routinely employed were not capable of detecting small differences. Thus, circulation times determined with

TABLE 1.—Results of Treatment in 100 Patients

Results	Number of Patients *
Notable improvement .....	35
Slight improvement .....	32 (2)
No change .....	28 (5)
Worse .....	5 (8)

\* Figures in brackets indicate the number of diabetic patients.

the fluorescein quartz lamp<sup>9</sup> showed improvement when the other methods revealed no change. The subject of the patient's peace of mind will be discussed later. For the sake of uniformity, however, improvement was only noted when one or several of our tests indicated it; subjective improvement without objective evidence of improvement was disregarded (table 1).

According to this table, 67 patients derived some benefit whereas 33 patients either showed no improvement or had a progression of the disease. For such a heterogenous group of patients as these, the figures require further analysis. For the sake of brevity only some of the more obvious factors have been analyzed. The grading of peripheral vascular involvement is shown in table 2. One notes that 71 patients had an advanced degree of obliteration, and this is to be expected since our indications call for more active types of therapy, notably sympathectomy, for patients in the earlier stages of the disease. The duration of treatment as it influenced results has also been of interest, and table 3 indicates that approximately two thirds of the 100 patients had

9. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, *M. Clin. North America* 26:943, 1942.

less than one year of treatment whereas one third continued to use the apparatus for over one year. The figures are small, but the percentage of failures after one year is about one third of that observed among patients who stopped the treatment before the year was over. There are, of course, several factors here which cloud the issue. The fact that the patients continued treatment for more than a year indicates that they had a favorable response earlier since otherwise they would have discontinued it. The patients were told not to continue treat-

TABLE 2.—*The Severity of Vascular Disease in 100 Patients*

Grade 1.....	2
Grade 2.....	27
Grade 3.....	41
Grade 4.....	30
	<hr/> 100

TABLE 3.—*Results as Influenced by Duration of Treatment*

Duration of Treatment	Number of Cases	No Improve- ment	Percentage Not Improved
1 to 3 mo.....	28	11	39
3 to 6 mo.....	17 67	9	53 41
6 to 12 mo.....	22	7	32
1 to 3 yr.....	21	6	29
3 to 6 yr.....	11 33	2	18 15
More than 6 years.....	1	..	0
	<hr/> 100	<hr/> 35	

TABLE 4.—*Results as Influenced by Diabetes*

Case	Age	Grade	Subjective Relief	Objective Relief	Worse
A.B.....	58	3	None	None	..
G.A.....	65	3	None	None	+
R.T.....	53	3	None	None	+
S.D.....	48	4	None	None	..
S.L.....	56	4	Moderate	Slight	..
L.L.....	65	3	None	None	..
O.S.....	51	2	None	None	..
S.B.....	65	4	Slight	None	..
M.B.....	55	2	Slight	Slight	..
R.S.....	48	4	None	None	+

ment if after one or two months there was no subjective improvement. On the basis of table 3, we are inclined to believe that such treatment, once it is clearly indicated and prescribed, should be continued for one year before it is permanently given up.

We have already stated that diabetic arteriosclerosis, especially when associated with diabetic neuropathy, responds poorly to intermittent venous hyperemia. In table 4 we have listed data on 10 diabetic patients, all of whom have used this treatment for at least three months.

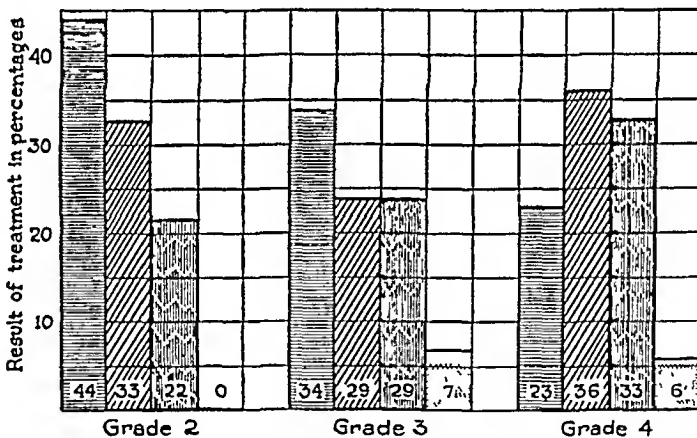
Only 2 of the 10 have shown objective improvement. In a number of other cases, not included here, the treatment was discontinued after a few days because of continuous pain or lancinating, pseudotabetic pain.

Table 5 shows the degree of improvement in the 100 cases according to the four grades of severity of the disease. If the 2 patients with grade 1 disease, who both did well, are disregarded, one can say that with advancing degree of obliteration fewer patients can expect decided improvement. Roughly speaking, a little less than one half of the patients with grade 2 disease showed considerable improvement (12 of

TABLE 5.—Results as Influenced by Stage of Vascular Disease

Grade	Number of Cases	Notable Improvement	Slight Improvement *	No Change *	Worse *
1	2	2	0	0	0
2	27	12	9 (1)	6 (1)	0
3	41	14	12	12 (1)	3 (2)
4	30	7	11 (1)	10 (3)	2 (1)
	100	35	32 (2)	28 (5)	5 (3)

\* Figures in brackets indicate the number of diabetic patients.



Results of the use of a rhythmic constrictor for the production of intermittent venous hyperemia. Note that for grade 2 disease the percentage of improvement is higher than for grade 3 disease and that it is less for grade 4. Note also that the incidence of lack of improvement or of no change is greatest among patients classified as having grade 4 disease. These findings would indicate that the results of treatment are obviously dependent on the degree of vascular sclerosis present. First column signifies considerable improvement, second column slight improvement, third column no change and fourth column worse.

27, or 44 per cent) and about one third of the patients with grade 3 disease showed notable improvement (14 of 41, or 23 per cent). Given in the form of a chart, the data illustrate what a patient may expect when he starts using this apparatus provided acute vascular occlusions or trauma<sup>10</sup> does not accelerate the progress of his disease.

10. Trauma is used in the broadest sense of the word and includes not only mechanical trauma but thermal, chemical, toxic and psychic trauma as well.

## COMMENT

From the start, our idea was to supply the patient suffering from advanced obliterative vascular disease with a simple inexpensive type of treatment which could be used at home for a long time without interfering with his work. It is true that absolute rest in a hospital, preferably on an oscillating bed, is superior to any type of conservative management. On our service this treatment is reserved for patients in a pregangrenous or gangrenous state who have continuous pain at rest, with pronounced edema of the foot and ankle; and who sit up all night hanging their feet down and thereby getting some relief. Extremities can be saved by this method. The material studied here, however, is of a different nature. These are ambulatory patients with intermittent claudication, numbness and tingling of the toes, often associated with angina pectoris, who have been told in the past that nothing can be done for them but that they must simply await the unpredictable progression of an incurable disease. To the patient, this often means that gangrene will develop and that he is doomed to lose his leg since that is what he saw happen in some older members of his family. If the rhythmic constrictor did nothing else but supply the patient with a harmless placebo, it would fulfill a need in geriatric practice.

Our experience, however, with individual cases extending as long as ten years has convinced us of the definite value of this method. We are well aware of the pitfalls of evaluating the merits of any method for the treatment of peripheral vascular disease. There are factors which are difficult to control, i. e., spontaneous improvement, sudden exacerbation of the local fault, acute vascular accidents elsewhere, the effect of seasonal variations in temperature and humidity and the effect of other forms of treatment such as, for instance, abstinence from tobacco. In addition, we have lately used sympathetic ganglionectomy extensively in the treatment of both Buerger's disease and peripheral vascular sclerosis,<sup>11</sup> and we see no reason why patients whose vasoconstrictor tone is abolished should not get additional benefit from intermittent venous hyperemia.<sup>1</sup> In fact, we routinely use this method for patients who have undergone sympathectomy.

In this series, however, we eliminated all outside factors so far as possible. There were no patients with thromboangiitis obliterans included and the patients with arteriosclerosis had either stopped smoking before treatment or were permitted to smoke in moderation. "Theocalcin" (mixture of calcium theobromine and calcium salicylate) or aminophyl-

11. de Takats, G., and Evoy, M. H.: Sympathectomy for Peripheral Vascular Sclerosis, J. A. M. A. 133:441 (Feb. 15) 1947.



line was routinely given to all patients for their coronary circulation,<sup>12</sup> but we have no evidence that there is any decided peripheral effect unless theobromine is given intravenously, and then it is of an evanescent nature.<sup>13</sup>

There is considerable controversy as to the mechanism whereby intermittent venous compression acts<sup>14</sup>; we have not concerned ourselves in this clinical paper with such considerations. However, our original contention that in addition to a small reactive hyperemia a mechanical filling and stretching of the terminal vascular bed takes place must be obvious to anyone who watches a foot under treatment. This may be undesirable in certain forms of arteriolar disease with veno-capillary congestion and stasis, and such a situation contraindicates this treatment.

Observations, then, relating to temperature of the skin, rapidity of blood flow and circulation times before and after a single treatment cannot measure the true value of intermittent venous hyperemia. Clinical observations on controlled material extending over a period of one to several years have been recorded here; they encouraged us to continue this form of therapy as an adjuvant to surgical methods.

#### SUMMARY

A series of 100 patients have been studied who have received treatment with intermittent venous hyperemia for several months or years exclusive of all other methods of treatment.

The data have been analyzed in regard to severity of the disease and duration of treatment. With less severe vascular obliteration and with longer periods of treatment, the results improved.

Improvement was measured by objective methods of which the most sensitive was found to be venous filling time and walking ability.

Diabetic patients with involvement of the peripheral nerves, patients with pronounced vascular spasm and those with arteriolar and capillary stasis are not suitable subjects. Patients with vascular sclerosis in whom the preliminary tests show poor response to sympathectomy or those who have already undergone sympathectomy but still have considerable claudication constitute the group for whom this form of treatment is indicated. It is intended for ambulatory patients, to be used in the home for a period of at least one year with the object of arresting or slowing down a progressive peripheral vascular sclerosis.

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12. Gilbert, N. C., and Kerr, J. A.: Clinical Results in the Treatment of Angina Pectoris with the Purine-Base Diuretics, *J. A. M. A.* **92**:201 (Jan. 19) 1929.

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# PANCREATIC CALCIFICATION

Study of Clinical and Roentgenologic Data on Thirty-Nine Cases

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**B**Y THE TERM "pancreatic calcification" we refer to calcareous deposits in the pancreas, either within the ducts or in the parenchymatous tissue outside the ducts or in both. From a practical clinical standpoint the inclusive term "pancreatic calcification" seems preferable to the term "calculi." Accordingly, we have refrained from using the word "calculi" in order to avoid the possible implication that calcific deposits are necessarily located within the ducts.

Pancreatic calcification was apparently first reported by Graaf<sup>1</sup> in 1667. Haggard and Kirtley<sup>2</sup> in 1939 reviewed the incidence for a period of two hundred and seventy-one years and could find authentic records of only 204 cases. Mayo<sup>2a</sup> reported on 25 proved cases of pancreatic calculi at the Mayo Clinic prior to 1936. That this complication of pancreatic disease is being recognized with increasing frequency is evidenced by the fact that prior to 1925 only 102 cases were reported whereas from 1925 to 1942 inclusive 118 cases were reported in the literature.<sup>3</sup> Snell and Comfort<sup>4</sup> have also pointed out the fact that pancreatic calcification is being recognized with increased frequency.

## OBJECTIVES AND PLAN OF STUDY

The objectives of the present analysis were (1) to study the symptomatology and the roentgenologic features in cases of pancreatic calcification and (2) to learn whether there is any correlation between the extent of calcification in the pancreas and the incidence of clinical

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1. Graaf, cited by Haggard and Kirtley.<sup>2</sup>

2. Haggard, W. D., and Kirtley, J. A., Jr.: Pancreatic Calculi: A Review of Sixty-Five Operative and One Hundred and Thirty-Nine Nonoperative Cases, *Ann. Surg.* **109**:809-824 (May) 1939.

2a. Mayo, J. G.: Pancreatic Calculi, *Proc. Staff Meet., Mayo Clin.* **11**:456-457, 1936.

3. Jaleski, T. C.: Pancreatic Lithiasis, *Ann. Int. Med.* **20**:940-947 (June) 1944.

4. Snell, A. M., and Comfort, M. W.: The Incidence and Diagnosis of Pancreatic Lithiasis: Review of Eighteen Cases, *Am. J. Digest. Dis.* **8**:237-243 (July) 1941.

manifestations, with particular reference to the manifestations of other complications of pancreatic disease such as diabetes mellitus and steatorrhea.

Evidence of pancreatic calcification is primarily a matter of roentgenologic diagnosis in the absence of surgical or postmortem examination of the pancreas since there are no symptoms or signs by which calcification can be diagnosed. In view of this fact, we studied the roentgenologic and clinical features of patients who on roentgenologic examination were found at the Mayo Clinic in the years 1939 to 1943 inclusive to have pancreatic calcification.

#### ANALYSIS OF DATA

*Relation Between Calcification and Pancreatitis.*—There were 39 cases in which, in the opinion of one of us (D. G. P.), the criteria for the roentgenologic diagnosis of pancreatic calcification were fulfilled.

TABLE 1.—*Incidence of Pancreatitis in Thirty-Nine Cases of Pancreatic Calcification*

Group	Pancreatitis	Cases	
		Number	Percentage
1.....	Proved	22	56
2.....	Probable	4	10
3.....	Possible	8	21
4.....	Negative history	5	13

When the records of these cases were studied it was found that with reference to the diagnosis of pancreatitis the patients could be conveniently divided into four groups, namely, (1) those who had proved pancreatitis, (2) those who had probable but unproved pancreatitis, (3) those who had possible pancreatitis and (4) those who had no symptoms at any time which were in any way suggestive of pancreatitis (table 1).

Although the criteria which were used for the diagnosis of pancreatitis in this series of cases have been described in previous reports,<sup>5</sup> a brief summary of them is indicated at this point. A diagnosis of relapsing pancreatitis is justifiable in the presence of recurrent severe attacks of pain in the upper part of the abdomen commonly lasting for hours or days and often requiring the administration of more than one hypodermic injection of opiate, provided other causes for such attacks

5. (a) Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: A Study of Twenty-Nine Cases Without Associated Disease of the Biliary or Gastro-Intestinal Tract, *Gastroenterology* 6:239-285 (April); 376-408 (May) 1946. (b) Gambill, E. E.; Comfort, M. W., and Baggenstoss, A. H.: Unpublished data.

have been excluded and there is evidence of one or more of the following: (a) steatorrhea not otherwise explained, (b) pancreatic calcification on roentgenologic examination or on surgical exploration or at necropsy, (c) supernormal concentration of amylase or lipase in the blood serum, (d) an enlarged, hard, nodular, edematous pancreas observed at surgical exploration and (e) leukocytic infiltration, interstitial fibrosis, residual necrosis, atrophy, calcification, pseudocysts and abscess formation in pancreatic tissue obtained for biopsy or at necropsy. Although pain is often severe and prolonged, it is not always so; in some instances it may be relatively mild and atypical.

In this series group 1 was made up of 22 cases, or 56 per cent of the total. In 19 of these the diagnosis of pancreatitis was proved by the findings at operation or necropsy. In the 3 remaining cases of this group the criteria for the diagnosis of pancreatitis which were summarized in the preceding paragraph were satisfied.

Group 2 consisted of 4 cases, or 10 per cent of the total, and included those in which the patients had probable but not proved pancreatitis. In these cases there was a history of recurrent attacks of severe pain in the upper part of the abdomen which required opiates for relief and were suggestive of pancreatitis. Roentgenographic study of the gallbladder, stomach and duodenum had failed to disclose in those organs evidence of disease sufficient to explain the pain.

Group 3, which consisted of 8 cases, or 21 per cent of the total, included those in which the history was compatible with that obtained in the usual case of pancreatitis but was not typical. In 4 of the 8 cases there was a history of acute severe pain in the upper part of the abdomen, but the details were too poorly remembered to be of much clinical value. In the remaining 4 cases of this group there were complaints of pain in the upper part of the abdomen which were related particularly to alimentation but were not suggestive of pancreatitis. Flatulent dyspepsia and at times anorexia and nausea were experienced.

Group 4, which was composed of 5 cases, or 13 per cent of the total, comprised those in which no history suggestive of pancreatitis was given. One patient complained of mild pain and soreness in the right upper part of the abdomen which were relieved by lying down or by sitting. None of the other 4 patients of this group gave any history of abdominal pain. Gaseous dyspepsia and constipation were noted by 2 patients. One must keep in mind the possibility that the patients in this group could have had one or more relatively mild, unremembered episodes of acute pancreatitis in early life. Another possibility is that calcium had been deposited in the pancreas of these persons in response to a low grade, subclinical pancreatitis in a manner analogous to that of the deposition of calcium in the lung or lymph nodes in tuberculosis.

It would appear from these findings that pancreatic calcification is usually associated with a history of pancreatitis but not necessarily always.

*Sex.*—Of the 39 patients, 28, or 72 per cent, were males and 11 were females, a ratio of 2.5:1.0. The predominance of males over females has been observed also in chronic pancreatitis, in which a ratio of 4.3:1.0 was noted in 56 cases.<sup>5</sup>

*Age.*—In the 39 cases of pancreatic calcification the median age at the time that calcification was first discovered was 43 years; the youngest age was 10 years and the oldest 70 years.

In 21 of the 22 cases of proved pancreatitis in which data were available the median age at which seizures first appeared was 30 years, the youngest age 10 years and the oldest age 65 years. Thus in one half of the cases the painful seizures began before the patient was 30 years old.

*Weight.*—Patients were of approximately normal weight for their height and age. Those who suffered from frequent severe episodes of pain and in whom diabetes mellitus or steatorrhea developed frequently lost between 15 and 20 per cent of their original weight.

*Painful Seizures Associated with Pancreatic Calcification.*—Precipitating Causes: The possible influence of trauma, exercise and alcohol in the precipitation of the attacks of pain of pancreatitis has been discussed in previous studies.<sup>6</sup> In 1 case of proved pancreatitis the first attack of pain came while the patient was playing baseball. These attacks continued to recur two to four times a year. Pancreatic calcification was discovered three years after the initial attack of pain. In another case of proved pancreatitis the patient remarked that yelling, running or lifting tended to induce the attacks of pain. In 5 of the 22 cases of proved pancreatitis the use of alcohol seemed to precipitate the attacks.

*Duration and Frequency of Occurrence of Attacks of Pain:* The time which had elapsed since the onset of seizures of pain varied from two months to twenty-two years, with an average of 6.6 years. The seizures lasted from one hour to three weeks. Repeated hypodermic injections of morphine were often needed to control the pain. The frequency of occurrence of seizures varied from five weekly to one every six years. The general tendency was for the attacks to become increasingly frequent, severe and prolonged with the passage of time.

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6. Myers, W. K., and Keefer, C. S.: Acute Pancreatic Necrosis in Acute and Chronic Alcoholism, *New England J. Med.* **210**:1376-1380 (June 28) 1934. Weiner, H. A., and Tennant, R.: A Statistical Study of Acute Hemorrhagic Pancreatitis (Hemorrhagic Necrosis of Pancreas), *Am. J. M. Sc.* **196**:167-176 (Aug.) 1938. Footnote 5a and b.

In a few cases, however, the attacks tended to become less severe after a few years. We wish to make it clear that we regard the attacks of pain primarily as manifestations of pancreatitis rather than of calcification.

**Interval Between Occurrence of First Painful Seizure and Discovery of Calcification:** The time that elapsed between the occurrence of the first painful seizure and the discovery of calcification, diabetes mellitus and pancreatic steatorrhea is given in table 2. While in about one fifth of the cases calcification was noted a year after the onset of attacks of pains, in another fifth calcification was not apparent until eleven to twenty-two years after. Likewise, the intervals between the onset of severe pain and the discovery of diabetes or steatorrhea varied widely.

**Relation of Site of Calcification to Site of Pain:** Reasoning that pancreatic calcification is most commonly the result of previous inflam-

TABLE 2.—*Years Between Onset of Attacks of Severe Pain and the Discovery of Pancreatic Calcification, Diabetes Mellitus and Steatorrhea \**

Years	Calcification, Number of Cases	Diabetes, Number of Cases	Steatorrhea, Number of Cases
1.....	8	3	1
2 to 10.....	17	3	4
11 to 22.....	8	3	2
Unknown.....	2	0	0
No pain.....	4	0	0

\* Based on 39 cases of pancreatic calcification.

mation and that pain during the attacks is due to inflammation or edema, we attempted to see if there was any association between the site of calcification in the pancreas and the primary site of pain during the acute seizures. In general it was found that when calcification was limited to the head of the pancreas the pain was usually felt first in the right upper part of the abdomen or in the epigastrium whereas when the calcification was present throughout the pancreas the pain more often than not was felt first in the epigastrium. While in some cases pain was confined to the initial or primary site, in many it was also propagated to other regions so that the entire upper region of the abdomen became involved.

**Associated Complications.**—Complications which were found in association with pancreatic calcification were diabetes mellitus, steatorrhea, gastrointestinal hemorrhage, morphinism, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis (table 3).

**Diabetes Mellitus and Steatorrhea:** In 5 cases of the 10 in which diabetes developed the disease appeared within three years after the

onset of painful seizures. Occasionally diabetes mellitus or steatorrhea did not appear until after many years of recurrent attacks of pancreatitis. While it is doubtful whether calcification as such has much to do with the development of diabetes, proof is lacking to substantiate this doubt. The destruction of the islet tissue by repeated attacks of acute inflammation with or without necrosis would seem to be a more reasonable theory for the causation of instances of diabetes.

TABLE 3.—*Complications Associated with Pancreatic Calcification*

Complication	Cases	
	Number *	Percentage *
Diabetes mellitus.....	9	23
Pancreatic steatorrhea.....	7	18
Gastrointestinal hemorrhage.....	3	8
Morphinism.....	8	8
Inflammatory pancreatic pseudocyst.....	2	5
Pancreatic abscess.....	1	3
Peripheral neuritis.....	1	8

\* Based on 39 cases of pancreatic calcification.

The incidence of diabetes or steatorrhea or of both in cases of pancreatic calcification was much greater among patients who gave a history suggestive of pancreatitis than among those who did not. As a matter of fact, in this series diabetes or steatorrhea or both occurred only in cases of calcification in which there was an associated history

TABLE 4.—*Incidence of Diabetes and Steatorrhea in the Presence of Pancreatic Calcification With and Without a History of Pancreatitis \**

History of Pancreatitis	Pancreatic Calcification				Steatorrhea	
	Cases	Diabetes			Cases	Percentage
Positive.....	22	Cases	Percentage		7	32
Negative or doubtful.....	17	9	41		0	0
		0	0			

\* Based on 39 cases of pancreatic calcification.

of pancreatitis (table 4). The evidence indicates, therefore, that when calcification is found in a case of chronic relapsing pancreatitis it is prone to be associated with serious impairment in pancreatic function indicative of advanced disease. On the contrary, pancreatic calcification which is discovered, accidentally or otherwise, in a person who gives no previous history of pancreatitis or a questionable one is generally not prone to be associated with any gross disturbances in pancreatic function.

As might be anticipated, there seemed to be a high degree of positive correlation between the extent of calcification in the pancreas and the

incidence of diabetes and steatorrhea. Thus in 23 cases in which the calcification was limited to the head of the pancreas only 4 instances of diabetes or steatorrhea occurred, whereas in 11 cases in which calcification involved the entire pancreas there were 9 instances of diabetes or steatorrhea.

It should be emphasized, however, that extensive pancreatic calcification is not always associated with signs of pancreatic insufficiency, as is illustrated by 1 case (fig. 1). The patient suffered from one attack of pain suggestive of gallstone colic ten years before admission to the

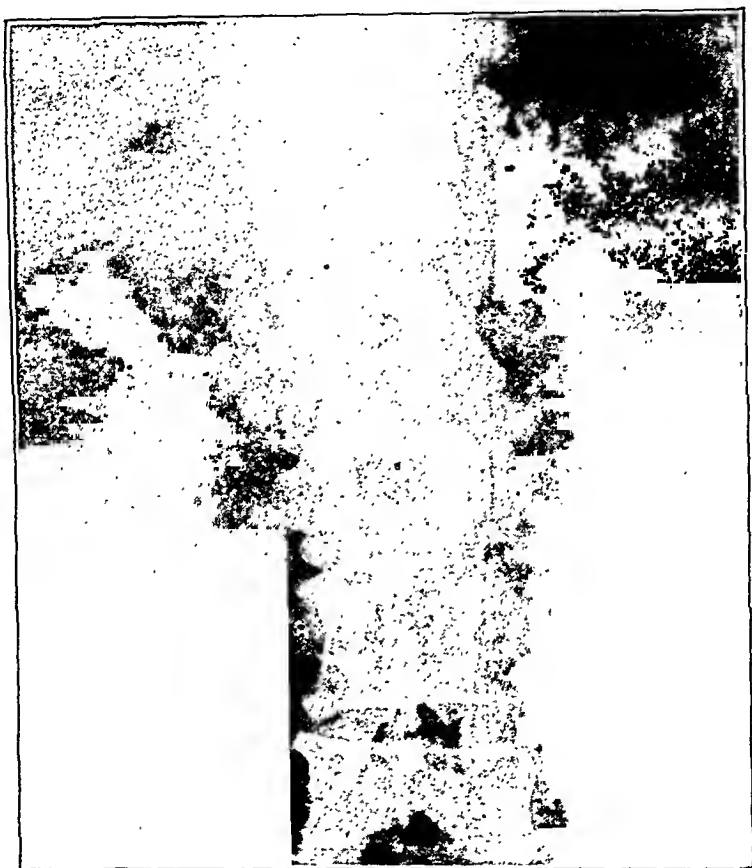


Fig. 1.—Possible pancreatitis. There is extensive calcification throughout the pancreas.

clinic. There had been no indigestion for seven years prior to admission. The cholecystogram did not reveal disease of the gallbladder but demonstrated pancreatic calcification. There were no symptoms or signs of pancreatic insufficiency; however, no tests were performed to detect any possible subclinical deficiency.

There appeared to be no positive correlation between the size, shape or method of grouping of the calcareous deposits and the degree of pancreatic insufficiency. Moreover, the extent of calcification and the degree of disturbance of pancreatic function were not necessarily related



to the length of time during which a patient had been suffering from the severe seizures of pain.

**Gross Gastrointestinal Hemorrhage:** Gross bleeding from the upper part of the gastrointestinal tract in the absence of demonstrable peptic ulceration or of other gross lesions of the esophagus, stomach, duodenum or liver has been observed in patients who have pancreatitis. Because of the frequent occurrence of the factor of alcoholism, it has been suspected that such bleeding may possibly be due to alcoholic gastritis.<sup>5</sup> In this series of 39 cases of calcification 3 patients had a history of gross hemorrhages from the upper part of the gastrointestinal tract. One patient suffered from recurrent gross hematemesis. He used alcohol chronically. Physical, roentgenographic and gastroscopic examinations were noncontributory. At exploration the surgeon found chronic pancreatitis but no evidence of any lesion of the stomach or duodenum.

Another patient suffered from recurrent hematemesis and melena. He likewise was a heavy user of alcohol. Roentgenograms of the stomach and duodenum did not reveal any disease. At exploration the surgeon found severe chronic pancreatitis, with pancreatic pseudocyst and abscess in the lesser peritoneal sac, but no gross lesions of the stomach or duodenum.

The third patient, who had severe chronic pancreatitis with diabetes and steatorrhea, had become addicted to the use of alcohol and morphine. While residing in a hospital in an effort to get rid of the addiction to opiates, he experienced a gastrointestinal hemorrhage which was fatal. Necropsy revealed that a spicule of calcium in the head of the pancreas had apparently eroded through the duodenum, thus causing the fatal hemorrhage.

**Morphinism:** While morphinism is not strictly a complication specific for pancreatitis, it may result from the use of morphine for relief of the frequent exacerbations of severe pain. Consequently it may be difficult for the clinician to assess how much of the syndrome is due to results of addiction to morphine and how much to pancreatitis. In this series of 39 cases of pancreatic calcification there were definitely 2 and probably 3 patients who were addicted to opiates. Two of these patients had to go to an institution because of such addiction, which had been induced by the use of opiates for relief of the frequent and severe attacks of pancreatitis.

**Pancreatic Pseudocysts:** In this series of cases two pseudocysts occurred. They appeared to be the result of acute pancreatitis with necrosis and not secondary to calcareous deposits within the ducts.

**Pancreatic Abscess:** In 1 case of this series two abscesses were observed in the tail of the pancreas at necropsy. These were the result

of acute pancreatitis with necrosis. In another case an abscess developed in the lesser peritoneal sac as a result of acute pancreatitis with necrosis.

**Peripheral Neuritis:** Peripheral neuritis developed in 1 patient who also had pancreatic calcification, diabetes mellitus and steatorrhea as complications of chronic pancreatitis. The exact etiologic basis for the neuritis in this case was not clear, although it appeared to be largely the result of severe malnutrition and diabetes.

*Röntgenographic Aspects.*—Calcareous deposits in the pancreas are almost always rather dense and therefore radiopaque. For this reason the roentgenologic diagnosis can be made with accuracy,<sup>7</sup> and the clinical diagnosis is dependent on this fact. In many instances it is the repeated painful seizures that eventually lead to the suspicion of pancreatitis and to the discovery of pancreatic calcification. Frequently the clinician may suspect the presence of gallstones and may make a cholecystogram only to find a normally functioning gallbladder and calcification in the pancreas. Occasionally pancreatic calcification is accidentally discovered at the time of roentgenologic study of the stomach, duodenum or colon. Roentgenographic study of the kidneys or of the lumbar vertebrae may commonly disclose the presence of unsuspected pancreatic calcification. It is in the group with unsuspected disease that the diagnosis of calcification is most important, since such a diagnosis may direct attention to pancreatic disease that might otherwise remain unrecognized.

Any roentgenograms that include all or part of the pancreatic region may reveal calcareous deposits. In this series the deposits were seen most frequently, perhaps, in cholecystograms (fig. 2) or in localized roentgenograms of the gallbladder region (fig. 3). They were also discovered during roentgenologic examination of the gastrointestinal tract. In some instances roentgenograms of the abdomen or of the urinary tract revealed their presence (figs. 4 and 5). In roentgenograms of the lumbar vertebrae they were seen not only with the anteroposterior projection but also with the lateral and oblique views (fig. 5). If the presence of pancreatic calcareous deposits is suspected, localized anteroposterior, oblique and lateral roentgenograms of the area centered around the first and second lumbar vertebrae are most helpful. The pancreas varies somewhat in its location depending on the patient's habitus, but in this series calcareous shadows were seen most frequently at the level of the first and second lumbar vertebrae. At times

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7. Case, J. T.: Roentgenology of Pancreatic Disease: Caldwell Lecture, 1939, Am. J. Roentgenol. **44**:485-518 (Oct.) 1940. Gillies, C. L.: Pancreatic Lithiasis, with Report of a Case, Am. J. Roentgenol. **41**:42-46 (Jan.) 1939. McCullough, J. A. L., and Sutherland, C. G.: Intra-Abdominal Calcification: Interpretation of Its Roentgenologic Manifestations, Radiology **36**:450-457 (April) 1941.



Fig. 2.—Possible pancreatitis. There are irregular dense calcareous deposits in the head of the pancreas and a normally functioning gallbladder.



Fig. 3.—Proved pancreatitis. Calcification is present in the head of the pancreas and in part of the body.

they were seen as high as the level of the eleventh thoracic vertebra or as low as the level of the third lumbar vertebra. Calcification was present in various sites in the pancreas, but it was seen most frequently in the head just to the right of the spinal column (figs. 2 and 3). At times calcification was situated in the head or body of the pancreas



Fig. 4.—Proved pancreatitis. Calcification is present throughout the pancreas.



Fig. 5.—Proved pancreatitis. *a*, extensive calcification, especially in the tail of the pancreas; *b*, lateral view; *c*, oblique view.

overlying the vertebrae, and thus calcific shadows were occasionally difficult to see. Oblique and lateral roentgenograms were of assistance in such instances (fig. 5). It is important that the roentgenograms cover the entire pancreatic region since otherwise small localized shadows of calcification, particularly if situated in the tail of the pancreas, may be missed. In a few cases there was extensive calcification throughout the

gland from head to tail, and in such cases the shape of the pancreas was well shown in the roentgenograms (figs. 1, 4 and 6).

Deposits of calcium in the pancreas varied greatly in shape and size (fig. 3). In some cases they were tiny, being only a few millimeters in diameter. Numerous small calcific shadows of this type were usually present when there was extensive involvement of the entire gland. Larger, well circumscribed deposits were encountered; these occurred most commonly in the head or body of the pancreas. Shadows of calcification were sometimes seen which had the appearance of irregular, conglomerate masses of calcium. In rare instances extremely large calcareous shadows, at times several centimeters in diameter, were seen. The finding of faceted stones in the duct of Wirsung has been reported, but this is extremely unusual. Calcareous deposits of different shapes and sizes were often seen in the same gland.



Fig. 6.—Proved pancreatitis. *a*, cholecystogram in 1935 revealed no pancreatic calcification and a functioning gallbladder; *b*, calcification throughout the pancreas in 1940.

In some instances the roentgenologic diagnosis of pancreatic calcification can be made with ease because of the location, size, shape and density of the calcareous deposits. However, other conditions which produce calcific shadows in the upper part of the abdomen must be differentiated from pancreatic calcification. Gallstones are frequently faceted, are more laterally situated and are not often so densely calcified as are calcific deposits in the pancreas. Occasionally in the cholecystogram the gallbladder appears to overlie the vertebrae; it is possible that gallstones in a gallbladder located in that position might resemble calcareous deposits in the pancreas. Stones in the common bile duct could be difficult to distinguish from calcific shadows in the pancreas, but the former are seldom densely calcified. Renal calculi are seen somewhat lateral to the pancreatic region. It is conceivable that renal calculi in a horseshoe kidney could be mistaken for pancreatic calcification. Calcified mesenteric nodes in the region of the head of the pancreas may be difficult to distinguish from calcification within the

pancreas, but as a rule the so-called mulberry appearance of calcified nodes and their presence in other parts of the abdomen make possible the correct diagnosis. Calcification of the suprarenal gland can usually be identified by its location and shape.

Calcification of the abdominal aorta is linear and can be easily identified in the lateral view. Calcification of the arteries of the celiac axis is seen as linear, crescentic or annular shadows of calcification. Localized calcification of the vertebral ligaments or calcification of the nucleus pulposus may be seen at the level of the head of the pancreas, but these should cause no confusion. At times special examinations, such as cholecystography and excretory urography, are necessary before a definite diagnosis can be made. Roentgenologic study after the stomach and duodenum have been filled with barium will aid in showing the relationship of calcareous shadows to the pancreatic region. However, special studies of this type are seldom necessary.

*Treatment.*—The indications for treatment of pancreatic calcification are primarily those employed for the treatment of pancreatitis, which we believe is the most common precursor of calcification.

Medical treatment seems to have little effect in preventing the painful exacerbations or in arresting the progress of the disease. A bland diet relatively low in fat, the abstinence from alcoholic excesses and the avoidance of excessive nervous and physical stress were advised, but there was no real evidence that these measures had any effect in reducing the frequency of occurrence or the severity of painful seizures. Whenever indicated, insulin was employed for diabetes mellitus and pancreatin for pancreatic steatorrhea. The diabetes was relatively mild. In instances of steatorrhea it was noted that the amount of fat lost in the feces could be materially reduced by the use of pancreatin in appropriate amounts, usually from 2 to 10 Gm. three times a day. There were 9 cases of diabetes mellitus and 7 cases of steatorrhea. In 21 of the 39 cases operation was not performed.

For those who are afflicted with frequent attacks of severe pain surgical intervention is the treatment of choice, although it is not always effective in stopping the attacks of pain and the results in a given case are unpredictable. Surgical intervention was carried out in 18 of the 39 cases of this series for one or more of the following reasons: (1) to arrest the progress of the disease or at least to try to reduce or abolish the frequency of occurrence and the severity of the painful seizures, (2) to relieve obstruction of the duodenum or of the common bile duct due to an enlarged pancreas, (3) to remove calcareous masses which might possibly be obstructing the exit of the main pancreatic duct and (4) to drain or remove pseudocysts or abscesses of the pancreas. While any type of treatment may give discouraging

results and while the effectiveness of any given treatment is unpredictable, about two fifths of the patients who suffered from recurrent attacks of pain were completely relieved and about one fifth were partially relieved of the acute seizures for significant periods after certain surgical procedures designed to promote prolonged internal or external drainage of the common bile duct had been carried out. These procedures were cholecystogastrostomy, cholecystojejunostomy, choledochoduodenostomy and external drainage of the common bile duct by means of a T tube for at least six to twelve months. Of these, we are inclined to favor prolonged T tube drainage or, preferably, choledochoduodenostomy when that operation is feasible.

Pancreatolithotomy was performed on 1 patient; the surgeon removed some calcareous masses in and around the exit of the major pancreatic ducts. This procedure followed by roentgen therapy applied over the pancreatic region resulted in cessation of the painful seizures. Partial or total pancreatectomy was not employed in any of the cases of this series: We doubt that such procedures are justifiable except for patients who have severe and irreparable pancreatic insufficiency and who are invalidated by intractable pain.

*End Results.*—No immediate surgical deaths occurred among the 18 cases in which operation was performed. One patient died, approximately three years after leaving the clinic, of a subhepatic abscess, which was thought to be secondary to leakage at the site of cholecystogastrostomy, which had been done previously for pancreatitis. Another patient, who had not had surgical treatment, died a month after leaving the clinic. Necropsy was reported to show chronic pancreatitis with calcification, two abscesses in the pancreas and acute vegetative endocarditis. A third patient died of a massive gastrointestinal hemorrhage as the result of erosion through the wall of the duodenum by a spicule of calcium in the pancreas.

In a few cases spontaneous amelioration of the painful seizures occurred, and in others the disease progressed in spite of all efforts by the clinician and the surgeon. In still others the severity of the disease did not change. Some patients became almost incapacitated for work, undernourished and addicted to opiates. Others turned to alcohol for spurious relief of what seemed to be a hopeless plight. The necessity for frequent hospitalization, numerous surgical operations and payment of medical bills and the inability to work constituted a serious economic, mental and emotional strain which sapped the morale of some of the patients.

#### SUMMARY

In a study of 39 cases of pancreatic calcification, selected solely on the basis of roentgenologic evidence of calcification, it was found that

calcareous deposits in the pancreas were usually but not always associated with relapsing pancreatitis. Commonly the symptomatology was that of pancreatitis, although in approximately two fifths of the cases there was either no history of pancreatitis or a doubtful one. Among cases in which a definite history of pancreatitis was obtained, calcification became evident in a fifth in one year after the onset of pain, but in another fifth calcification was not discovered until after eleven to twenty-two years.

Associated complications in the order of frequency of occurrence were diabetes, steatorrhea, gastrointestinal hemorrhage, morphinism, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis.

There was a high degree of positive correlation between the extent of pancreatic calcification and the incidence of two other complications associated with pancreatic calcification, namely, diabetes and steatorrhea. Diabetes and steatorrhea occurred only in cases of calcification in which there was a definite diagnosis of pancreatitis.



## INSULIN ALLERGY

Treatment With the Histamine Antagonists

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### INCIDENCE OF INSULIN ALLERGY

**I**NSULIN allergy, the antigenic response to the insulin protein, is a rare but important occurrence in diabetic management. The incidence of allergic reactions to insulin varies widely in the reports in the literature. Some observers considered mild local reactions as allergic manifestations. Others were found to exclude all local reactions regardless of severity and to designate as allergic only those patients for whom insulin therapy had to be discontinued. Hence such wide variations as Grafe's<sup>1</sup> 0.15 per cent, Collens'<sup>2</sup> 7.3 per cent and Allan and Scherer's<sup>3</sup> 11.7 per cent were reported. Of persons sensitive to insulin, Allan and Scherer estimate that from 98 to 99 per cent will show a reaction limited to the site of injection while only 1 or 2 per cent will exhibit general or systemic manifestations. Thus, approximately one in a thousand using insulin will have a generalized reaction.

Mild local reactions usually disappear within two weeks of the onset of therapy. These reactions are believed to be due to extraneous material within the preparation and not to the insulin itself. A change in the brand of insulin is frequently all that is necessary to do away with this reaction.

Insulin allergy causes a local reaction of increasing severity. A generalized urticaria accompanied with severe pruritus appears. Other common manifestations are angioneurotic edema, arthralgia, gastrointestinal symptoms, bronchial asthma and circulatory failure. Less frequently generalized erythemas, pruritus without urticaria and eruptions

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1. Grafe, E.: Probleme der Insulintherapie, München. med. Wchnschr. **83**: 1255-1258, 1936.

2. Collens, W. S.; Lerner, G., and Fialka, S. M.: Insulin Allergy: Treatment with Histamin, Am. J. M. Sc. **188**:528-533, 1934.

3. Allan, F. N., and Scherer, I. R.: Insulin Allergy, Endocrinology **16**: 417-430, 1932.

of a morbilliform, scarlatiniform or vesicular type are seen. Occasionally insensitivity to the antidiabetic activity of insulin is demonstrated.

Allan and Scherer<sup>3</sup> reported their experiences with 100 cases of insulin allergy observed at the Mayo Clinic. Of the 100 patients, 84 showed a mild local reaction. This was usually seen between the third and fourteenth days of therapy. In 12 instances there were severe local reactions lasting one or more weeks. In only 4 cases were generalized reactions seen; these consisted of cutaneous, circulatory and gastrointestinal symptoms.

#### INSULIN IS A PROTEIN

That the crystalline pure hormone insulin is a protein is definitely established. Abel<sup>4</sup> described the preparation of pure crystalline insulin and found that its chemical reactions were characteristic of protein substances. Examining the crystalline insulin derived from the pancreas of various animals (ox, sheep, hog and fish), he found them to have similar microscopic appearances, solubilities, isoelectric points and carbon, hydrogen, nitrogen and sulfur content. Jensen,<sup>5</sup> in chemical studies of insulin, was able to derive numerous amino acids from it and also found that its reactions were characteristic of protein substances.

#### ANTIGENIC ACTIVITY OF INSULIN

The antigenic activity of insulin has been demonstrated experimentally by various workers. Barral and Roux<sup>6</sup> found that the sensitization following the injection of insulin is specific for the hormone itself and is not related to that produced by proteins of beef serum or beef pancreas. Wassermann and others<sup>7</sup> demonstrated that insulin is antigenic. Serums from sensitized rabbits gave positive reactions to complement fixation tests. Bernstein, Kirsner and Turner<sup>8</sup> have shown that guinea pigs given parenteral injections with commercial and crystalline insulin reacted with anaphylaxis to subsequent intravenous injections. Raynaud and Lacroix<sup>9</sup> were able to demonstrate the presence of precipitins in the blood serum of an allergic patient. They were also able to sensitize a guinea pig with insulin and then produce ana-

4. Abel, J. J.: Crystalline Insulin, *Proc. Nat. Acad. Sc.* **12**:132-136, 1926.

5. Jensen, H.: Chemical Study of Insulin, *Science* **75**:614-618, 1932.

6. Barral, P., and Roux, J.: L'insuline constitue-t-elle en elle-même un antigène spécifique? *Compt. rend. Soc. de biol.* **106**:292-293, 1931.

7. Wassermann, P.; Broh-Kahn, R. H., and Mirsky, I. A.: Antigenic Property of Insulin, *J. Immunol.* **38**:213-219, 1940.

8. Bernstein, C., Jr.; Kirsner, J. B., and Turner, W. J.: Studies on Anaphylaxis with Insulin, *J. Lab. & Clin. Med.* **23**:938-944, 1938.

9. Raynaud, A., and Lacroix, A.: Anaphylactic Shock from Insulin: Pathogenesis of Insulin Edema, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:831, 1925

phylactic shock by injection of the blood serum of an allergic patient. Lewis,<sup>10</sup> using the Schultz-Dale uterine muscle technic to study the antigenic properties of insulin, found that the muscle strips sensitized to beef insulin did not react in the presence of beef pancreas or beef serum but did react to beef insulin. Cross reactions were obtained between beef and pork insulin.

#### IMPORTANCE OF INSULIN ALLERGY

No fatal immediate reactions following the use of insulin have been reported. However, several deaths have been attributed indirectly to insulin allergy.

Goldner and Ricketts<sup>11</sup> reported a case in which insulin allergy acted as a contributory cause of death. The patient, who had mild diabetes, was allowed to go untreated. Subsequent bronchopneumonia precipitated severe acidosis. Efficient antidiabetic therapy could not be instituted, and death resulted. Lereboullet<sup>12</sup> treated a 4 year old diabetic child who at first responded well to insulin. She was given measles convalescent serum and diphtheria prophylaxis. Subsequently, each injection of insulin was followed by urticaria and by generalized edema. The symptoms abated when administration of insulin was stopped, but they recurred even with a change of brand. When measles developed, diabetic coma followed. Attempted desensitization resulted in general urticaria and edema. Insulin allergy was a factor in the fatal outcome.

Failure to respond to insulin may be the result of insulin allergy. Thus, Glassberg and others<sup>13</sup> described a patient who was resistant to insulin therapy and required 300 units daily. Injections of insulin from various animal sources resulted in severe local reactions. Desensitization with insulin was followed by gradual diminution in the refractoriness. Karr, Scull and Petty<sup>14</sup> reported the development of extensive local induration following injections of insulin, accompanied with severe insulin refractoriness. After the subsidence of the reaction, the amount of insulin required was markedly reduced. Foerster<sup>15</sup> reported on a patient who used insulin with benefit and then discontinued using it. When therapy was commenced once more, the insulin

10. Lewis, J. H.: Antigenic Properties of Insulin, *J. A. M. A.* **108**:1336-1338 (April 17) 1937.

11. Goldner, M. G., and Ricketts, H. T.: Insulin Allergy: Report of Eight Cases with General Symptoms, *J. Clin. Endocrinol.* **2**:595-602, 1942.

12. Lereboullet, P.; Lelong, M., and Frossard, R.: Eruptions Under Insulin Treatment, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:1184-1190, 1924.

13. Glassberg, B. Y.; Somogyi, M., and Taussig, A. E.: Diabetes Mellitus: Report of Case Refractory to Insulin, *Arch. Int. Med.* **40**:676-685 (Nov.) 1927.

14. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, *J. Lab. & Clin. Med.* **18**:1203-1211, 1933.

15. Foerster, E.: Paradoxical Action of Insulin, *Med. Klin.* **22**:846-849, 1926.

proved ineffective, and considerable glycosuria and acetonuria were observed. Generalized urticaria occurred. Insulin in large doses failed to bring about the anticipated effect. Foerster expressed the belief that the insulin allergy interfered in some way with the action of the insulin hormone. Grote's<sup>16</sup> patient showed an increasing tolerance to insulin. After a period of latency there was a sudden urticarial attack. When the usual dose of insulin was given, hyperglycemia, glycosuria and ketosis developed. More insulin was required for control.

Insulin refractoriness is not a constant accompaniment of insulin allergy. Allen and Scherer<sup>3</sup> as well as Herzstein and Pollack<sup>17</sup> reported no change in the physiologic action of insulin in their cases.

#### TREATMENT OF INSULIN ALLERGY

Many of the local reactions following the injection of insulin are not allergic. Thus, with the removal of impurities which were present in earlier products fewer reactions occurred. Alcohol used in the sterilization of the syringe and the formaldehyde in the cleansing alcohol have been incriminated.

Injection of the insulin deeply into the subcutaneous tissue, the changing of the brand of insulin to one derived from another animal source, or the employment of crystalline insulin are all effective means of combating reactions except when insulin allergy exists.

In the specific management of insulin allergy, varying degrees of success have been reported with desensitization. Methods are described by Allan and Scherer,<sup>3</sup> Bayer<sup>18</sup> and Corcoran<sup>19</sup> for rapid desensitization. Slow desensitization is reported by Bryce<sup>20</sup> and by Herold.<sup>21</sup>

Nonspecific measures, too, have been used in an attempt to control insulin allergy. Hunscheidt<sup>22</sup> suggested injection of calcium with the insulin. Strasser<sup>23</sup> administered calcium prior to the insulin. Collens<sup>2</sup> reported on the use of histamine three times weekly in gradually increas-

16. Grote, I. R.: *Neuzeitliche Diabetesbehandlung, Ergebn. d. ges. Med.* **18**: 301-458, 1933.

17. Herzstein, J., and Pollack, H.: *Insulin Allergy: Case Report with Review of Literature, J. Mt. Sinai Hosp.* **6**:3-17, 1939.

18. Bayer, L. M.: *Desensitization to Insulin Allergy, J. A. M. A.* **102**:1934-1936 (June 9) 1934.

19. Corcoran, A. C.: *Note on Rapid Desensitization in Case of Hypersensitiveness to Insulin, Am. J. M. Sc.* **196**:359-361, 1938.

20. Bryce, L. M.: *Hypersensitiveness to Insulin, M. J. Australia* **1**:371-376, 1933.

21. Herold, A. A.: *Insulin Allergy: Report of Severe Case with Successful Desensitization, New Orleans M. & S. J.* **91**:163-166, 1938.

22. Hunscheidt, H.: *Calcium bei Insulinüberempfindlichkeit, Zentralbl. f. inn. Med.* **55**:369-371, 1934.

23. Strasser, A.: *Insulinbehandlung unter Kalkaufladung, Med. Klin.* **27**: 695, 1931.

ing doses. Roth<sup>24</sup> reported good results in the elimination of local reactions to insulin by the daily oral administration of histaminase. Karr<sup>14</sup> suggested sensitization of a rabbit with the serum of the patient allergic to insulin. The rabbit's serum was then used in an attempt to desensitize the patient.

Recently Gastineau and Leavitt<sup>25</sup> reported the use of "benadryl hydrochloride" in the treatment of a case of insulin allergy. The patient presented local as well as generalized lesions. "Benadryl administered orally afforded almost complete relief of local and generalized urticaria, while a dilute solution of benadryl mixed with insulin prevented local reactions."

#### THE HISTAMINE ANTAGONISTS

The histamine antagonists present new hope for the control of allergic manifestations. In 1937 Edlbacher, Jucker and Bauer<sup>26</sup> demonstrated the action of the amino acids histidine, cysteine and arginine in inhibiting the histamine-stimulated contraction of the guinea pig intestine. Landau and Gay<sup>27</sup> found the toxicity of these substances high and their efficacy low.

Fourneau,<sup>28</sup> working in France as early as 1910, prepared phenolic ethers of amino alcohols and later demonstrated their antihistamine reaction. Halpern<sup>29</sup> in 1942 prepared a series of related compounds. One of these substances, "antergan," and, more recently, "neoantergan" have received enthusiastic support in the French literature.

In this country investigative work for the production of efficacious antihistaminic drugs has resulted in tripeleennamine hydrochloride, or "pyribenzamine hydrochloride" (N. N. R.), diphenhydramine hydrochloride, or "benadryl hydrochloride" (N. N. R.). Structural for-

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24. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, *Bull. New York Acad. Med.* **16**: 570-584, 1940.

25. Gastineau, C. F., and Leavitt, M. D.: Treatment of Allergy to Insulin with Benadryl: Report of One Case, *Proc. Staff Meet., Mayo Clin.* **21**:316-319, 1946.

26. Edlbacher, S.; Jucker, P., and Bauer, H.: Die Beeinflussung der Darmreaktion des Histamins durch Aminosäuren, *Ztschr. f. physiol. Chem.* **247**:63, 1937.

27. Landau, S. W., and Gay, L. N.: Influence of Certain Amino Acids on Histaminé Reactions and Anaphylactic Reactions in Intestinal Strips of Guinea Pigs and in Intact Guinea Pigs, *Bull. Johns Hopkins Hosp.* **74**:55-76, 1944.

28. Fourneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau dérivé du dioxane, *Arch. internat. de pharmacodyn. et de thérap.* **46**:178-191, 1933.

29. Halpern, B. N.: Etude expérimentale des antihistaminiques de synthèse; essais de chimiothérapie des états allergiques, *J. de méd. de Lyon* **23**:409-411, 1942.

mulas reveal the similarity of these compounds. Tripeleennamine hydrochloride differs from "antergan" only by the substitution of the pyridil ring for the phenyl and from "neoantergan" by the omission of the methoxy group.

Loew and Kaiser<sup>30</sup> demonstrated the value of the synthetic benzhydryl alkamine ethers in alleviating both histamine shock and anaphylactic shock in guinea pigs. Wells, Morris, Bull and Dragstedt<sup>31</sup> suggest that the action of these drugs is to attach themselves to some of the receptors on the cells which would ordinarily be occupied by the histamine molecules.

Recently the opportunity presented itself for the clinical trial of the antihistamine drugs in the treatment of a patient with insulin allergy.

#### REPORT OF A CASE

A. B., a 46 year old housewife, was first admitted to the Boston City Hospital in April 1946. Studies revealed persistent glycosuria, acetonuria and hyperglycemia. A diet of 110 Gm. of carbohydrate, 50 Gm. of protein and 50 Gm. of fat was ineffectual in controlling her diabetes. One week after her admission to the hospital the patient was started on 10 units of protamine zinc insulin. A local reaction of moderate intensity appeared after the first injection. Each subsequent day the reaction increased in severity. Tenderness, local heat, swelling and redness were present, and they persisted for periods greater than twenty-four hours.

One week after the onset of the insulin therapy, a generalized urticarial rash appeared. The cutaneous lesions spontaneously disappeared at the end of four hours. The use of protamine zinc insulin was continued, and two days later an acute attack of nausea, vomiting and weakness was noted.

After two and one-half weeks of hospitalization the patient was discharged. She was taking 20 units of protamine zinc insulin. Local reactions at the site of the inoculation were of moderate severity.

In the following month the severity of the local reaction increased. Urticaria recurred on a number of occasions and was described as generalized and severe. Nervousness and arthralgia were noted. There were frequent episodes of nausea and vomiting. The patient discontinued taking insulin and subsequently became asymptomatic. She was advised to return to the hospital for desensitization, but because of her illness of the previous month she decided on a vacation.

In October 1946 she returned to the hospital, complaining of weakness and fatigue. The fasting blood sugar content was 235 mg. per hundred cubic centimeters, and hospitalization was once more recommended.

With the patient on a diet of 121 Gm. of carbohydrate, 53 Gm. of protein and 64 Gm. of fat, the hyperglycemia, glycosuria and acetonuria persisted. Cutaneous

30. Loew, E. R., and Kaiser, M. E.: Alleviation of Anaphylactic Shock in Guinea Pigs with Synthetic Benzhydryl Alkamine Ethers, *Proc. Soc. Exper. Biol. & Med.* **58**:235-237, 1945.

31. Wells, J. A.; Morris, H. C.; Bull, H. B., and Dragstedt, C. A.: Observations on Nature of Antagonism of Histamine by B-Dimethylaminoethyl Benzhydryl Ether (Benadryl), *J. Pharmacol. & Exper. Therap.* **85**:122-128, 1945.

tests were done, with the use of numerous brands of commercial insulin <sup>32</sup> (0.05 cc. containing 1 unit of insulin injected intradermally). Crystalline zinc insulin, regular insulin, globin insulin and protamine zinc insulin were used. In each instance an indurated urticarial wheal developed, surrounded by an erythematous irregular flare. The wheal persisted, although somewhat diminished, for twenty-four hours.

A dermal passive transfer test of the skin was carried out. One tenth of a cubic centimeter of the patient's serum was injected subcutaneously into the forearm of 3 normal persons. Into the other forearm a similar injection of normal serum was made. Twenty-four hours later 0.05 cc. of crystalline insulin was injected intradermally into the sensitized and nonsensitized areas. Within fifteen minutes each of the sensitized areas showed pronounced wheal and flare. This reaction continued to increase in intensity for thirty to sixty minutes and then began to fade.

Attempt to control the diabetes was made subsequently by using globin insulin and then crystalline insulin. With each product the previously described experience of severe local reaction with generalized urticaria was repeated.

It became apparent that if this patient was to receive insulin therapy it would be necessary to desensitize her or to administer concurrently a histamine antagonist. Because of the frequent failures of the former method, it was decided to use the latter.

"Benadryl hydrochloride" in a 100 mg. daily dose produced drowsiness. "Pyribenzamine hydrochloride" was substituted, and no disagreeable side reactions were noted. A dosage of 150 mg. daily was used initially. This was increased to 350 mg. A schedule of 50 mg. every three hours was found to be the most efficacious.

Protamine zinc insulin <sup>33</sup> (25 units administered in the morning) initially was found to produce a moderate reaction. This was neither as severe nor as persistent as the previous reactions. With the increased dosage of the antihistamine drug, the local reaction diminished. Within three days, in which time the maximum dosage of "pyribenzamine hydrochloride" was reached, the local reaction was negligible. No generalized reactions or constitutional symptoms were noted.

In order to evaluate further the effect of the "pyribenzamine hydrochloride" and because evidence of glycosuria was observed in the evening specimens of urine, a second daily injection of regular insulin was decided on. A brand of insulin was chosen which produced the most pronounced intradermal reaction.<sup>34</sup> Ten units was given at noon. With this dose, a mild local reaction was noted at the site of the injection for the next three days. However, this decreased in severity, and eventually no reaction followed the injection of either insulin.

After two weeks of therapy, no localized or generalized reactions to either regular insulin or protamine zinc insulin were noted. Results of determinations of the blood sugar content and of urinalysis attested to the controlled diabetic state. The cutaneous tests were repeated, the same products being used as in the previous tests. The immediate reaction was more intense; the wheals and flares were larger, and pseudopods were present. The wheals subsided rapidly, the swelling, erythema and pruritus remaining for twenty-four hours.

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32. Iletin (Eli Lilly and Company), iletin (Eli Lilly and Company) made from zinc insulin crystals; protamine, zinc and iletin (Eli Lilly and Company); insulin (E. R. Squibb & Sons); protamine zinc insulin (E. R. Squibb and Sons); insulin (Sharp and Dohme, Inc.); protamine zinc insulin (Sharp and Dohme, Inc.); globin insulin with zinc (Burroughs Wellcome & Co.).

33. Sharpe & Dohme, Inc.

34. Insulin (Sharpe & Dohme, Inc.).

At the end of three weeks, during which time the patient was entirely asymptomatic and the diabetes was well controlled by the morning injection of protamine zinc insulin and the noon injection of regular insulin, the use of "pyribenzamine hydrochloride" was discontinued. That same evening the patient complained of a generalized pruritus. The following day swelling, induration, tenderness and pain appeared at the site of the injections of insulin and increased in severity. Small urticarial wheals soon appeared on the extremities. These coalesced into larger hives, and pruritus became severe. Similar larger lesions appeared on the abdomen. Urinalysis at this time showed a persistent orange-red reduction of Benedict's solution in four specimens.

On the following day the patient was once more given the 300 mg. daily dose of "pyribenzamine hydrochloride." Except for mild pruritus and induration at the site of the inoculation with insulin, she became asymptomatic again. Urinalysis now revealed blue and green reduction of Benedict's test solution. Within two days even the local reaction disappeared. At this point the following question arose: Was the histamine antagonist also preventing desensitization while preventing the allergic manifestations to insulin? With this in mind, it was decided to reduce progressively the dosage of the drug. By so doing it was hoped that the severe allergic manifestations would be prevented while a sufficient amount of the insulin would be free to cause a state of "desensitization."

Over a period of four weeks the amount of "pyribenzamine hydrochloride" given was gradually reduced until none was being used. The dosage was determined by the degree of the local reaction to the insulin. With each reduction there were noted local erythema, induration, swelling, pruritus and glycosuria. Maintenance of the reduced dosage soon resulted in the disappearance of the local reaction as well as of the glycosuria.

For the next month A.B. remained symptom free. No "pyribenzamine hydrochloride" was required. The diabetic state was well controlled by diet and by the daily injection of the two doses of insulin.

After this there was an occasional complaint of local pain, swelling and pruritus at the site of the inoculation of the protamine zinc insulin. Lesions which were about 2 cm. in diameter, mildly erythematous and moderately indurated were seen. The symptoms were at their maximum in six hours and entirely gone in twelve to twenty-four hours. "Pyribenzamine hydrochloride" in a single daily dose of 25 to 50 mg. was found to control the occasional local reaction.

The passive transfer test of the skin was repeated. A negative reaction was obtained, indicating either the absence of the skin-sensitizing antibodies in the patient's serum or their presence in but small amounts.

With her adherence to the prescribed diet, the patient's insulin was progressively reduced. The noon dose of regular insulin was discontinued, and the morning dose of protamine zinc insulin was reduced to 15 units. The diabetic state remained well controlled and the patient's general condition good.

#### COMMENT

Insulin allergy is reportedly on the increase. Allan and Scherer<sup>8</sup> stated the belief that this was due to sensitization to insulin given in previous years. The importance of the problem for the individual physician called on to treat the diabetic person who is allergic to insulin cannot be minimized.



With the availability of the histamine antagonists, a new method of therapy presents itself. Further clinical trial will be necessary, but that these new drugs have a prominent place in this problem is now apparent.

That "pyribenzamine hydrochloride" was able to control the allergic manifestations of insulin is well demonstrated in this case report. The recurrence of symptoms on withdrawal of the drug is further support of this.

The striking local reaction to the second series of cutaneous tests at a time when the patient was generally asymptomatic as a result of the use of "pyribenzamine hydrochloride" is in agreement with the findings of others. Thus Friedlaender and Feinberg<sup>35</sup> report that the ingestion of "benadryl hydrochloride" did not have any decisive effect on the whealing produced in scratch tests with serial dilutions of histamine or with ragweed extract in sensitive patients. However, when the histamine antagonist was mixed with the antigen or applied to scratches prior to the application of the urticariogenic agent, there was an inhibition of the whealing phenomenon. It would appear that after the oral ingestion of the histamine antagonist there could never be present a sufficient concentration to compete successfully for the receptor cells with the locally liberated histamine.

The development of a persistent glycosuria accompanying the allergic manifestations after withdrawal of the histamine antagonists raises the problem of the relation of insulin refractoriness to allergy. The cases of Glassberg, Foerster and Karr are cited previously. Rudy<sup>36</sup> reports on a patient with mild diabetes in whom an idiopathic urticaria developed and who then required 515 units of insulin in the next twenty-four hours. With the disappearance of the cutaneous lesions, the amount of insulin required was eventually reduced to 10 units on the eleventh day.

Root,<sup>37</sup> working with depancreatized dogs, calculated that 200 to 300 units of insulin would be required by a man of average weight. In cases in which larger amounts are required the disease is considered refractory. Some of the mechanisms producing this state are:

1. Lack of absorption due to induration of the tissues, sclerosis of the vessels or defective circulation.

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35. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: Effect of Oral and Local Use of  $\beta$ -Dimethylaminoethyl Benzhydryl Ether Hydrochloride on Whealing Due to Histamine, Antigen-Antibody Reactions, and Other Whealing Mechanisms, Therapeutic Results in Allergic Manifestations, *J. Allergy* **17**:129-141, 1946.

36. Rudy, A.: Urticaria and Insulin Resistance with Reference to Relation of Skin to Carbohydrate Metabolism: Report of Case and Review of Literature, *New England J. Med.* **204**:791-796, 1931.

37. Root, H. F.: Insulin Resistance and Bronze Diabetes, *New England J. Med.* **201**:201-206, 1929.

2. Absence of some other essential factor in the process of glyco-genesis, i. e., the co-enzyme of Glassberg,<sup>13</sup> the phosphates described by Markowitz<sup>38</sup> and the activating kinase of Himsworth.<sup>39</sup>

3. Loss of tissue in which glycogen can be stored, i. e., involvement of the liver in hemochromatosis, fatty deposition or necrosis.

4. Inhibition of insulin action by infection, pus and toxins. Fever causes an increased requirement.

5. The action of the endocrine antagonists of the pancreas, i. e., the pituitary, thyroid and adrenal glands.

6. Blockage of the diffusion of sugar into the skin. Folin,<sup>40</sup> working with animals, showed that after the intravenous injection of dextrose the skin played an important part in the distribution of sugar in the body. The skin was found to act as a reservoir for the increased amount of sugar. Root<sup>37</sup> concluded from Folin's observations that insulin refractoriness in diabetic patients with disorders of the skin may be caused by a blockage in the diffusion of the sugar into the diseased skin. An increased amount of insulin is required to reduce the elevated blood sugar content.

7. Neutralization of insulin. Lowell<sup>41</sup> presents evidence indicating the presence of two antibodies for crystalline insulin in a patient who was both allergic and resistant to crystalline insulin. A heat-labile allergic antibody which was capable of passively transferring skin sensitivity and an insulin-neutralizing antibody which was heat stabile and capable of destroying the physiologic effect of crystalline insulin were demonstrated. Human and crystalline insulins caused allergic manifestations of the skin, but refractoriness was present to crystalline insulin alone. This evidence, then, plus the knowledge that as well as resistance to insulin in the absence of allergy there can be allergy to insulin in the absence of resistance have led Lowell to conclude that insulin may stimulate the formation of two antibodies, one capable of neutralizing insulin.

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38. Markowitz, J.: Relationship of Phosphate and Carbohydrate Metabolism: Effect of Glucose on Excretion of Phosphate in Depancreatized Dogs, *Am. J. Physiol.* **76**:525-531, 1926.

39. Himsworth, H. P.: Activation of Insulin, *Lancet* **2**:935-936, 1932.

40. Folin, O.; Trimble, H. C., and Newman, L. H.: Distribution and Recovery of Glucose Injected into Animals, *J. Biol. Chem.* **75**:263-281, 1927.

41. Lowell, F. C.: Immunologic Studies in Insulin Resistance: Report of Case Exhibiting Variations in Resistance and Allergy to Insulin, *J. Clin. Investigation* **23**:225-231, 1944; Immunologic Studies in Insulin Resistance: Presence of Neutralizing Factor in Blood Exhibiting Some Characteristics of an Antibody, *ibid.* **23**:233-240, 1944; Evidence for Existence of Two Antibodies for Crystalline Insulin, *Proc. Soc. Exper. Biol. & Med.* **50**:167-172, 1942.

A. B., described in this paper, demonstrated the complete inhibition of allergic manifestations with the histamine antagonists. On withdrawal of the latter, not only did the evidences of allergy reappear but so did glycosuria. Because the diabetes was mild, nothing further was noted.

Recommencing the use of the antihistamine drugs resulted in a rapid disappearance of the glycosuria. During the process of desensitization, with reduction of the amount of "pyribenzamine hydrochloride" used, increasing amounts of urinary sugar paralleled the local reaction.

This evidence suggests that the antihistamine agents are of value in some cases of insulin refractoriness associated with insulin allergy. The mechanism of production of the refractoriness may be the local allergic reaction. This tissue response preventing the absorption of the insulin results in an uncontrolled diabetic state. The importance of the antihistaminic agents in preventing these local reactions and thus allowing the free absorption of insulin is readily apparent.

In the case cited in this paper the condition remained well controlled and the patient asymptomatic while the histamine antagonists were being used to control the allergic manifestations of the insulin. At the end of three weeks it was felt that spontaneous desensitization would not occur. Feinberg<sup>42</sup> stated: "Although the preliminary experimental observations of others would indicate that the antagonists of histamine do not interfere with the antigen-antibody reaction or with desensitization, this question has not been conclusively settled." This, then, was the reason for progressively reducing the dosage of "pyribenzamine hydrochloride" to the level at which mild local symptoms were present. Small amounts of the antigen, it was presumed, would remain free to stimulate an antibody response.

That such a program is a successful method of treating insulin allergy is apparent. Whether one obtains complete "desensitization" or merely a state of "hyposensitization," the care of the patient becomes relatively simple. Small doses of the antihistamine drugs will easily control the occasional mild allergic manifestations.

A. B. showed occasional local reactions only at the site of the inoculation of the protamine zinc insulin. Taylor<sup>43</sup> and Wells<sup>44</sup> were unable to demonstrate any antigenic properties of the protamines. Yet the percentage of positive local reactions to protamine zinc insulin is greater

42. Feinberg, S. M.: Histamine and Antihistaminic Agents: Their Experimental and Therapeutic Status, *J. A. M. A.* **132**:702-713 (Nov. 23) 1946.

43. Taylor: Chemical Studies in Cytolysis, *J. Biol. Chem.* **5**:311-314, 1908-1909.

44. Wells, H. G.: The Chemical Aspects of Immunity, ed. 2, New York, The Chemical Catalog Company, 1929.

than that to any of the other types of insulin. Kern and Langner<sup>45</sup> expressed the opinion that the addition of protamine to insulin increases the allergy to the latter. Evidence is presented that the addition to a true antigen of a substance in itself possessing no antigenic properties makes sensitization to that antigen easier.

#### SUMMARY

1. The incidence of true insulin allergy is small. A generalized reaction develops in approximately one person in a thousand using insulin.

2. Insulin is a protein substance capable of antigenic activity.

3. The importance of insulin allergy is demonstrated by case reports from the literature.

4. Mention is made of the methods used in attempting to control insulin allergy.

5. Brief mention is made of the development of the histamine antagonists.

6. A case of insulin allergy is reported wherein the allergic manifestations were controlled with the newer histamine antagonists. A method for "hyposensitization" and, possibly, desensitization is described.

7. Insulin refractoriness associated with insulin allergy may be the result of impaired absorption from the site of injection due to local tissue reaction. Further investigation is awaited.

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45. Kern, R. A., and Langner, P. H., Jr.: Protamine and Allergy: Nature of Local Reactions After Injections of Protamine Zinc Insulin; Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin, *J. A. M. A.* **113**: 198-200 (July 15) 1939.

## HETEROPHILE ANTIBODY TITER IN DISEASES OTHER THAN INFECTIOUS MONONUCLEOSIS

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TO DATE, the heterophile antibody or Paul-Bunnell test has been considered one of the few specific laboratory tests, most investigators stating that only infectious mononucleosis, serum sickness or injections of liver can cause a diagnostic agglutination titer of 1:32 or higher by the Paul-Bunnell method or of 1:56 or higher by the more commonly used Davidsohn modified technic.<sup>1</sup>

In the laboratory of Research Hospital, my colleagues and I have in the past twenty-three months made a total of five hundred and three tests on 220 different patients, using exclusively the Davidsohn technic, with readings taken after overnight incubation in the refrigerator. Since many of these tests have been done on outpatients whose complete records were not accessible, the study is limited to 141 patients, representing only those for whom diagnosis was made after examination of tissue either on their admission to Research Hospital or on their examination at the Research Clinic. In this group of 141 patients are included 31 with clinically and/or hematologically proved infectious mononucleosis, 6 with Hodgkin's disease, 13 with leukemia of all types, 1 with polycythemia, 29 with tuberculosis, 8 with sarcoma other than Hodgkin's type and 53 with miscellaneous diseases in which there was no clinical or hematologic evidence of mononucleosis.

The table illustrates the frequency of various titers in the 31 patients with infectious mononucleosis and in the 57 with diseases other than infectious mononucleosis. The high incidence of the so-called diagnostic titers in diseases other than infectious mononucleosis is impressive.

The highest titers, of course, occur in infectious mononucleosis. What we wish to draw attention to, however, are the so-called diagnostic titers which have occurred in patients with other diseases.

### DIAGNOSTIC TITERS IN VARIOUS DISEASES

1. *Hodgkin's Disease*.—Kolmer and Boerner<sup>2</sup> stated: "Positive reactions do not occur in the leukemias, Hodgkin's disease, etc." However, in a total of eighteen tests on 6 patients examined here, we have

1. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, *Ann. Int. Med.* 2:230-251 (Aug.) 1944.

2. Kolmer, J. A., and Boerner, F.: *Approved Laboratory Technic*, ed. 4, New York, D. Appleton-Century Co., Inc., 1945, pp. 643-644.

found three agglutinations of 1:224, six agglutinations of 1:112 occurring in 2 different patients, seven agglutinations of 1:56 occurring in 6 different patients and no negative reading for any of the 6 patients. Sixteen of these eighteen tests are in the "diagnostic" range.

In this connection, Kaufman in 1944<sup>1</sup> reported that in his series of patients examined by the Davidsohn technic a rare titer of 1:112 was found in cases of scarlet fever, Hodgkin's disease and primary anemia, with also a titer of 1:224 in a case of Hodgkin's disease. He considered these results of no significance.

*Heterophile Antibody Titers in Infectious Mononucleosis and Other Diseases*

Disease	No. of Cases	No. of Readings	Frequency of Titers	No. of Readings in Diagnostic Range (1/56 or Higher)
Infectious mononucleosis .....	31	117	$\left\{ \begin{array}{l} 1 \times 14 \\ 3 \times 28 \\ 6 \times 56 \\ 16 \times 112 \\ 43 \times 224 \end{array} \right.$ $\left\{ \begin{array}{l} 37 \times 448 \\ 6 \times 896 \\ 3 \times 1,792 \\ 1 \times 3,584 \\ 1 \times 1,436 \end{array} \right.$	113 of 117
Hodgkin's disease .....	6	18	$\left\{ \begin{array}{l} 2 \times 7 \\ 7 \times 56 \end{array} \right.$ $\left\{ \begin{array}{l} 6 \times 112 \\ 3 \times 224 \end{array} \right.$	16 of 18
Agranulocytosis .....	3	10	$\left\{ \begin{array}{l} 3 \times \text{Neg.} \\ 2 \times 7 \\ 1 \times 14 \end{array} \right.$ $\left\{ \begin{array}{l} 2 \times 28 \\ 1 \times 56 \\ 1 \times 112 \end{array} \right.$	2 of 10
Lymphatic leukemia .....	2	8	$\left\{ \begin{array}{l} 1 \times 7 \\ 5 \times 14 \\ 2 \times 28 \end{array} \right.$	0 of 8
Monocytic leukemia .....	2	8	$\left\{ \begin{array}{l} 1 \times 14 \\ 1 \times 28 \\ 1 \times 56 \end{array} \right.$ $\left\{ \begin{array}{l} 4 \times 112 \\ 1 \times 448 \end{array} \right.$	6 of 8
Myelogenous leukemia .....	6	45	$\left\{ \begin{array}{l} 9 \times 7 \\ 6 \times 14 \\ 6 \times 28 \end{array} \right.$ $\left\{ \begin{array}{l} 17 \times 56 \\ 6 \times 112 \\ 1 \times 224 \end{array} \right.$	24 of 45
Polycythemia .....	1	3	$\left\{ \begin{array}{l} 1 \times 28 \\ 1 \times 56 \\ 1 \times 112 \end{array} \right.$	2 of 3
Sarcoma other than Hodgkin's Disease	8	23	$\left\{ \begin{array}{l} 11 \times \text{Neg.} \\ 3 \times 14 \\ 4 \times 56 \end{array} \right.$ $\left\{ \begin{array}{l} 3 \times 112 \\ 1 \times 224 \\ 1 \times 448 \end{array} \right.$	9 of 23
Tuberculosis .....	29	45	$\left\{ \begin{array}{l} 1 \times 14 \\ 17 \times 28 \\ 9 \times 56 \end{array} \right.$ $\left\{ \begin{array}{l} 10 \times 112 \\ 7 \times 224 \\ 1 \times 448 \end{array} \right.$	27 of 45

2. *Agranulocytosis*.—In a total of ten tests on 3 patients we found one agglutination at 1:112 and one at 1:56; there were three negative reactions, all of which occurred in a patient who in her fourth test had an agglutination of 1:7. In another case the sequence was 56, 112, 28, 14 and 7. Two of these ten titers are "diagnostic."

3. *Lymphatic Leukemia*.—In a total of eight readings on 2 patients we found no negative reactions but no agglutination over 1:28.

In this connection, Kent<sup>3</sup> reported in 1940 a case of fatal chronic myelogenous or chronic monocytic leukemia in a 14 year old boy with a 1:4096 titer by the original Paul-Bunnell technic (1:32 diagnostic).

3. Kent, C. F.: "False" Positive Paul-Bunnell (Heterophile) Reaction? *Am. J. Clin. Path.* 10:576-580 (Aug.) 1940.

He raised a question at that time in the title of his report: "'False' Positive Paul-Bunnell (Heterophile) Reaction?"

Furthermore, Bethell, Sturgis, Rundles and Meyers,<sup>4</sup> in a 1946 review of the literature on infectious mononucleosis, cited the report by Etcheverry of a titer of 1:896 in a case of lymphatic leukemia; the author attributed the titer to injections of liver which the patient had received.

4. *Monocytic Leukemia*.—In a total of eight readings on 2 patients with monocytic leukemia 1 of the patients had titers of 448, 112, 112, 112 in the four weeks prior to death and the other titers of 14, 28, 56, and 112, representing a progressive weekly rise till the time of death. Of these eight readings, six fall within the diagnostic range.

5. *Myelogenous Leukemia*.—Of a total of forty-five readings in 6 of our patients, twenty-four are in the diagnostic range. No correlation could be noted between the titers and any change in the differential counts of these patients.

As a matter of fact, in this group of cases is one of the early ones which stimulated interest in the "false" heterophile reaction. This is the case of a 42 year old man with a history of fever and chills for two days prior to his first admission to the hospital on April 10, 1946. A roentgenogram of the chest showed a possible atypical pneumonia. He was treated with sulfadiazine and penicillin and dismissed on April 13. When readmitted on July 6, he was complaining of pain in the chest, present ever since his previous discharge. His temperature was 100 to 101.8 F. Several examiners found no abnormal physical signs. The roentgenologic appearance of the chest was essentially the same as in April. The heterophile titer at which agglutination was positive on July 8 was 1:112; the blood count showed a hemoglobin content of 89 per cent; a red blood cell count of 4,400,000, and a white blood cell count of 12,700, with 27 segmented neutrophils, 12 stab forms, 11 eosinophils and 50 lymphocytes. Four days later, the heterophile agglutination was 1:224, with a white blood cell count of 16,250 now showing 17 segmented neutrophils, 17 stab forms, 1 juvenile form, 11 myelocytes, 4 premyelocytes, 6 eosinophils, 35 lymphocytes, 2 monocytes, 6 blastocytes, 1 unidentified cell and several smudges.

Several clinicians who saw the patient at this time persisted in the diagnosis of infectious mononucleosis because of the titers of 112 and 224; however, this titer then regressed to 56 on four readings, 28 on three readings and 14 on 1 reading, while the myelogenous series of cells gradually became more immature until he died on Sept. 16, 1946, of full-blown acute myelogenous leukemia.

4. Bethell, F. H.; Sturgis, C. C.; Rundles, R. W., and Meyers, M. C.: Blood: A Review of the Recent Literature; Infectious Mononucleosis; Arch. Int. Med. 77:80-91 (Jan.) 1946.

6. *Polycythemia*.—Two of our three readings taken in 1 case of polycythemia fall within the diagnostic range. Since there is only 1 case in this group, we can give this little if any statistical importance.

7. *Sarcoma Other Than Hodgkin's Disease*.—Nine of twenty-three readings on the 8 patients with sarcoma other than Hodgkin's type are in the diagnostic range. Interestingly, in 1 of 2 cases of reticulum cell sarcoma there were nine repeated negative readings, with never a positive reaction, while in the other the readings were 448, 224, 112 and negative. In 1 case of fibrosarcoma of the abdominal wall the titer was 1:112 on one occasion and 1:56 on two occasions, and in a case of follicular lymphoblastoma there was a reading of 1:112. The 1 patient with myxosarcoma in the group had two readings of 1:56 occurring simultaneously with a myelogenous leukemoid reaction in the peripheral blood smear. In the 3 cases of lymphosarcoma there were three readings at 1:14, one at 1:56, and one negative reaction.

8. *Tuberculosis*.—Since twenty-seven of our forty-five readings on 29 tuberculous patients are in the "diagnostic" range, we consider this an important statistical group. Two young men with fever and chills were found to have a titer of 1:224 with no other evidence of infectious mononucleosis. Both subsequently died after a brief stormy course of miliary tuberculosis. Since few patients with tuberculosis are admitted to Research Hospital, we obtained permission to select patients at the Leeds Tuberculosis Sanatorium for further study.

We selected 12 patients in the terminal stages of tuberculosis and another 12 who were ready to be dismissed with their disease completely arrested. In the terminal group we found 4 patients with a titer of 1:224, 4 with a titer of 1:112 and 4 with a titer of 1:28. In the arrested group, we found essentially the same, i. e., 2 patients with a titer of 1:224, 4 with a titer of 1:112, 3 with a titer of 1:56 and 3 with a titer of 1:28. Thus in all cases of tuberculosis, both active and arrested, which we have investigated there has been a positive titer, and in twenty-seven of forty-five tests on these 29 patients we have found a "diagnostic" level.

Bernstein<sup>5</sup> in 1940 wrote: "One of Longcope's cases developed tuberculous pleurisy six years later; a physician, not included in our group, died three year later of tuberculous meningitis. There is no reason to assume that these represent anything more than coincidences that might occur in any group of young people." Later in the same report, he says: "An occasional increased titer has been reported in scarlet fever, rubeola, tuberculosis and filariasis, but such events are excessively uncommon."

9. *Miscellaneous Diseases, With no Evidence of Infectious Mononucleosis*.—Throughout this study, patients with fever of any type or

5. Bernstein, A.: Infectious Mononucleosis, *Medicine* 19:85-159 (Feb.) 1940.



with a blood smear varying from the normal were candidates for the test. Some of our more interesting findings in this group were as follows: A titer of 1:224 was found in 1 case of allergy, 1 case of staphylococcemia from a carbuncle, a case of a 59 year old woman with a history of pleurisy and a diagnosis of tuberculosis in 1936 but with no evidence on roentgenologic examination at this time and a case of a 46 year old woman with evidence of old healed tuberculosis in a roentgenogram and with a monocyte count of 50 per cent. A titer of 1:112 was found in 1 case of toe infection due to *Staphylococcus albus* in a diabetic patient, thyrotoxicosis, splenic thrombocytopenia, chronic nephritis, aplastic anemia, diverticulitis of the colon, and migraine headache, in 1 patient receiving injections of liver and in 1 patient with quiescent rheumatic fever.

Agglutination in lower dilutions was obtained in a wide variety of cases.

#### COMMENT

From the data reviewed, we gain the impression that the heterophile antibody or Paul-Bunnell test is not as specific as it is generally considered to be. This statement is all the more interesting when the comment made by Paul and Bunnell themselves in their early report of 1932<sup>6</sup> is reviewed:

. . . in spite of the fact that the limits of the reaction which we have described have not been tested, it would seem to be of diagnostic value. In a sense, however, it appears to be of more theoretical than practical interest. Theoretical interest centers about the fact that heterophile antibodies may be produced or enhanced during the course of human infectious diseases, and in one disease in particular, in which the etiology has not been established. Furthermore, that 2 clinical entities with widely differing symptomatology, such as serum sickness and infectious mononucleosis, would elicit the same type of serologic response is also worthy of interest. . . . On the other hand, it is also conceivable that the phenomenon which we have described is in the nature of an isoagglutinin response to the presence of an excess of abnormal cells either present in the blood or elsewhere.

Our data would tend to bear out this last supposition, for all the diseases in our series which gave the so-called diagnostic titers—Hodgkin's disease and other sarcomas, blood dyscrasias and tuberculosis—are diseases characterized by abnormal cells present either in the blood or elsewhere.

#### SUMMARY AND CONCLUSIONS

1. Heterophile antibody titers were determined by the Davidsohn technic in a total of 57 patients suffering from Hodgkin's disease and other sarcomas, blood dyscrasias or tuberculosis.

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6. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, *Am. J. M. Sc.* **183**:90-104 (Jan.) 1932.

2. So-called diagnostic titers were found in a significant number of patients suffering from Hodgkin's disease, monocytic or myelogenous leukemia, several sarcomas and tuberculosis.

3. Patients showing a heterophile antibody titer of 1:56 or over and with no present or past clinical evidence of infectious mononucleosis or serum sickness deserve further study to determine the presence of organic disease. These diagnostic titers should not be dismissed as "incidental," but rather they should indicate, much in the manner of the increased sedimentation rate, further probing for a disease in which there are "abnormal cells present in the blood or elsewhere."

# MIXED INFECTION IN SUBACUTE BACTERIAL ENDOCARDITIS

Report of Two Cases

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**S**UBACUTE bacterial endocarditis caused by more than one micro-organism is uncommon. In 1942, Orgain and Poston<sup>1</sup> described 6 cases of mixed infection; since their report several additional cases<sup>2</sup> have been reported. The recognition of mixed infections is of more than theoretic interest in view of the present choice of antibiotics. Prompt treatment with the appropriate drug, in adequate dosage, can be facilitated when all the micro-organisms concerned in the infection are identified bacteriologically and when their sensitivities to the antibiotics are determined. These considerations apply to the 2 cases of mixed infection in subacute bacterial endocarditis recently encountered in Mount Sinai Hospital.

## REPORT OF CASES

CASE 1.—S. G., a 26 year old man, sought admission to the hospital for the first time on Sept. 7, 1946, because he had had a "blind spot" in the left eye for one week. At the age of 7 years the patient had had attacks of chorea, which recurred yearly until the age of 12. A residual cardiac murmur had been noted. For the past five years, the patient had had a slight elevation in blood pressure,

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From the Division of Bacteriology Laboratories and First Medical Service of Dr. George Baehr, The Mount Sinai Hospital, New York.

1. Orgain, E. S., and Poston, M. A.: Mixed Infections in Bacterial Endocarditis, *Am. Heart J.* **23**:823-836 (Dec.) 1942.

2. (a) Moore, R. A.: The Cellular Mechanism of Recovery After Treatment with Penicillin, *J. Lab. & Clin. Med.* **31**:1279-1293 (Dec.) 1946. (b) Favour, C. B.; Janeway, J. G.; Gibson, J. G., II, and Levine, S. A.: Progress in Treatment of Subacute Bacterial Endocarditis, *New England J. Med.* **234**:71-77 (Jan. 17) 1946. (c) Galbreath, W. R., and Hull, E.: Sulfonamide Therapy of Bacterial Endocarditis: Results in Forty-Two Cases, *Ann. Int. Med.* **18**:201-203 (Feb.) 1943. (d) Jones, S. H., and Tichy, F.: Bacterial Endocarditis Treated with Penicillin: Observations in Nine Cases, *New England J. Med.* **236**:729-736 (May 15) 1947. (e) Geiger, A. J.: Penicillin Therapy in Subacute Bacterial Endocarditis, *Mississippi Valley M. J.* **69**:2-16 (Jan.) 1947. (f) MacLean, H., and Howell, K. M.: Two Coexistent Strains of Viridans Streptococci Isolated from Blood Cultures by Penicillin Sensitivity Tests, *Am. J. M. Sc.* **214**:53-55, 1947. (g) Paul, O.; Bland, E. F., and White, P. D.: Bacterial Endocarditis, *New England J. Med.* **237**:349-354, 1947.

occasional periods of arrhythmia and tachycardia; the latter responded to treatment with digitalis.

Fever, chills, anorexia and cough began two weeks prior to admission. One week later, the patient noted impaired vision in the left eye. A tender node appeared in the left forefinger. Three hundred thousand Oxford units of penicillin in wax and oil were administered twenty-four hours prior to admission.

*Examination.*—On admission the patient was observed to be in good nutritional condition. His temperature was 101 F., pulse rate 120 and blood pressure 130 systolic and 70 diastolic. Vision was absent in the lower nasal field of the left eye. The fundus showed narrowing of the supertemporal artery, and there was slight retinal edema in the upper temporal quadrant of the affected eye. The heart was enlarged to the left. A coarse systolic murmur and thrill at the apex transmitted to the axilla, and an apical presystolic murmur and a diastolic murmur at Erb's

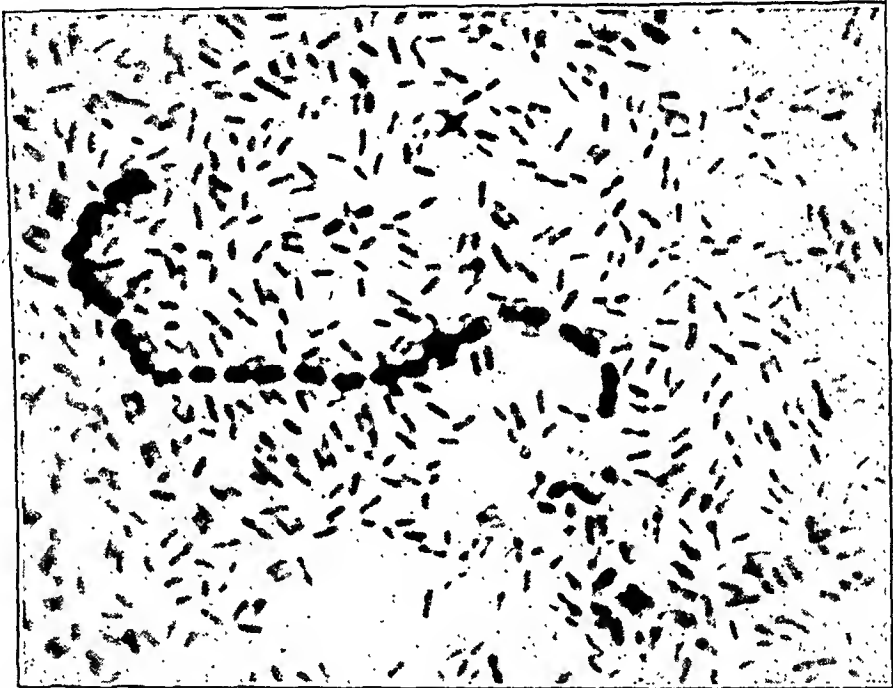


Fig. 1 (case 1).—*Str. viridans* and *C. pseudodiphthericum* (hoffmannii). Gram stain of a twenty-four hour subculture on blood agar plate from the original blood culture ( $\times 2,800$ ).

point were observed. The abdomen was normal. There was an Osler node at the tip of the left forefinger. The peripheral pulse had the bounding quality of a water hammer. Fluoroscopy confirmed the ventricular enlargement on the left side, prominent pulmonary artery segment, auricular enlargement on the left side and some cardiac enlargement on the right side. The electrocardiogram revealed regular sinus rhythm, wide and notched P waves and S-T elevation in all leads. The hemoglobin was 90 per cent (Sahli), red blood cell count 4,950,000 and white blood cell count 6,800, with 66 per cent segmented and 3 per cent nonsegmented polymorphonuclear leukocytes, 23 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The erythrocyte sedimentation rate was 44 mm. per hour (Westergren). The urine contained no albumin and no red blood cells. The level of urea nitrogen in the blood was 10 mg. and sugar 80 mg. per hundred cubic centimeters. The Wassermann reaction was negative, *Streptococcus viridans*

(alpha) was cultivated from the throat. Roentgenologic examination of the chest confirmed the fluoroscopic observations. Roentgenologic examination of the sinuses revealed evidence of chronic inflammation.

*Course.*—The patient continued to have a temperature between 101 and 102 F. for the following two weeks. The white blood cell count rose to 13,000, and evidence of a splenic infarct appeared, although the spleen itself was never palpable. The clinical diagnosis was subacute bacterial endocarditis. Repeated blood cultures were made in an effort to discover the responsible micro-organism before treatment was instituted.

*Bacteriologic Observations.*—The routine technic for blood cultures employed in the department of bacteriology of this hospital is as follows: Under strict aseptic conditions, 23 cc. of the patient's blood is drawn from an anterior cubital

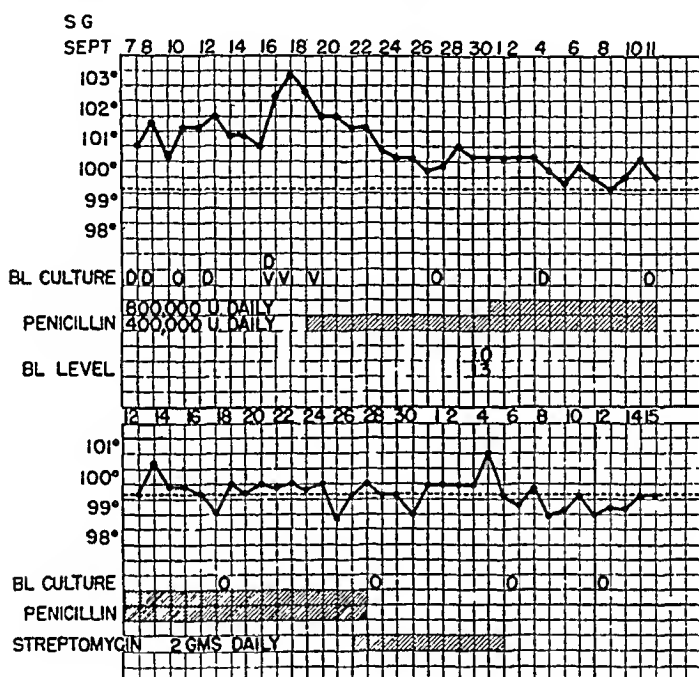


Fig. 2.—Summary of data in case 1.

vein; 15 cc. is divided equally among three 100 cc. Erlenmeyer flasks, the first containing yeast veal infusion broth at  $p_H$  7.4, the second, 2 per cent dextrose veal infusion broth at  $p_H$  7.4 and the third, plain veal infusion broth with para-aminobenzoic acid at  $p_H$  7.4. Two cubic centimeters of blood is mixed with each of two tubes containing 12 cc. of 2 per cent dextrose veal infusion agar at  $p_H$  7.4. Two cubic centimeters is mixed with a tube containing 12 cc. of plain veal infusion agar at  $p_H$  7.4, and 2 cc. is put into a tube containing 10 cc. of cooked liver broth at  $p_H$  7.4, which is sealed with 2 cc. of sterile petrolatum. The three flasks are kept in an atmosphere of air containing approximately 3.5 per cent of carbon dioxide, which is obtained by placing a lighted candle in a glass jar fitted with a petrolatum sealed cover.

Figure 2 demonstrates the significant observations in the blood cultures prior to and following treatment. Both diphtheroids and *Str. viridans* were obtained. The diphtheroids were short gram-positive bacilli in characteristic diphtheroid arrangement. The colonies were nonhemolytic, aerobic and facultatively anaerobic.

Glucose, sucrose, maltose, lactose and mannite were not fermented. There was no change in litmus milk, nor was gelatin liquefied. The streptococcus showed alpha hemolysis on the blood plate, was insoluble in bile, did not grow in 20 per cent bile broth or on Endo mediums and was killed by heating at 60 C. for twenty minutes.

At first the diphtheroids were considered to be contaminants, since they were not consistently cultured in all mediums. *Str. viridans* was finally isolated in the fifth, sixth and seventh blood cultures. The sensitivity of that organism to penicillin was as high as that of the standard strain, *Staphylococcus aureus* H, 0.02 units of penicillin per cubic centimeter being required for complete inhibition. Treatment was started with 400,000 Oxford units of penicillin daily, i. e., 50,000 Oxford units administered intramuscularly every three hours, on September 21. By the ninth day of treatment it was evident that the patient was not responding as well as might be expected from the high sensitivity of the organism. The dosage was therefore doubled to 800,000 Oxford units daily. The levels of penicillin in the blood fifteen minutes after administration of 100,000 Oxford units intramuscularly on two occasions were 1.0 and 1.3 units per cubic centimeter. Three hours after the injection was given, levels of 0.05 and 0.13 units per cubic centimeter were still present. With the increased dosage, the patient's temperature dropped to normal by the thirteenth day. On the same day, a diphtheroid was isolated once again. This organism was susceptible to 0.1 unit of penicillin per cubic centimeter, i. e., five times the resistance of the standard organism, and to 0.6 unit of streptomycin per cubic centimeter, i. e., three times the resistance of the standard organism, *Staph. aureus* (Smith). The diphtheroid was 50 per cent inhibited by 70 mg. per hundred cubic centimeters of sulfadiazine and not completely inhibited by 100 mg. per hundred cubic centimeters. It was identified as *Corynebacterium pseudodiphthericum* (hoffmannii). Since this was the fifth isolation of the diphtheroid, it was thought that this organism might be an additional infectious agent. The presence of diphtheroids also could explain the delayed response, in view of the fact that its resistance to penicillin was greater than that of *Str. viridans*. Treatment was continued for a total of six weeks. Twelve grams of streptomycin was given for six days, because of the susceptibility of the diphtheroids to streptomycin. Five subsequent blood cultures were negative. The patient was discharged on November 16. Additional blood cultures, made during return visits to the outpatient department, were sterile. The patient has been well for one year from the time of discharge.

*Comment.*—The pleomorphism of both organisms is well known.<sup>3</sup> It was necessary to eliminate the possibility that the diphtheroid and streptococcus forms were morphologic variants of one micro-organism. *C. pseudodiphthericum* and *Str. viridans* were therefore subcultured in broth and on solid mediums repeatedly for six weeks; the two organisms retained their morphologic and cultural characteristics. Review of the chart shows that the corynebacterium was isolated from five different blood cultures and *Str. viridans* from three different cultures. Furthermore, on one occasion both organisms were seen in the same

3. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, in Christian, H. A.: Oxford Loose-Leaf Medicine, New York, Oxford University Press, Inc., 1941. Jensen, L. B., and Morton, H. B.: The Diphtheroid Phase of Streptococci, *J. Infect. Dis.* 49:425 (Nov.) 1931.

culture. Thus, the evidence points toward mixed infection. The clinical course of the patient demonstrated that a dosage of penicillin ordinarily sufficient to inhibit the organism of lower resistance was inadequate to inhibit the organism of higher resistance in vivo.

CASE 2.—D. N., a woman aged 39, had had rheumatic fever at the age of 12 years. One month before the present admission, an infection of the upper part of the respiratory tract developed. Chills and fever, accompanied with loss of weight, cough and swelling and tenderness of the right middle finger, persisted until her admission on Nov. 2, 1946, despite six days of treatment with small doses of penicillin. A blood culture made one week prior to admission was negative.

*Examination.*—The temperature was 104 F., pulse rate 100, blood pressure 110 systolic and 55 diastolic and respiratory rate 20. Petechiae were seen in the left conjunctival sac and in the left fundus. A few moist rales were heard over the base of the left lung. The heart appeared enlarged to percussion, and murmurs of mitral and aortic insufficiency were present. The fingers were clubbed, and the left index finger was tender. There were petechiae on the right side of the chest, below the breast. Kyphoscoliosis of the dorsal and lumbar aspects of the spine, with convexity to the right side, was present.

*Laboratory Observations.*—The hemoglobin was 72 per cent, red blood cell count 3,900,000 and white blood cell count 23,900, with 72 per cent adult polymorphonuclear leukocytes, 14 per cent nonsegmented polymorphonuclear cells, 11 per cent lymphocytes and 3 per cent monocytes. The urine contained a trace of albumin and occasional white and red blood cells. The erythrocyte sedimentation rate was 48 mm. per hour (Westergren). The level of urea nitrogen in the blood was 11 mg. per hundred cubic centimeters. Venous pressure of the antecubital vein was 85 mm., and saccharine circulation time was 13 seconds. An electrocardiogram showed: regular sinus rhythm, left axis deviation, a small Q wave in leads I and II and a QRS interval of 0.11 to 0.12 seconds.

Figure 3 demonstrates the results of blood cultures, which revealed the presence of two different organisms. *Hemophilus parainfluenzae* was obtained on the first and third hospital days and *Str. viridans* on the second day. The first microorganism was a tiny gram-negative pleomorphic bacillus, which grew slowly aerobically, anaerobically and in 3.5 per cent carbon dioxide. In liquid mediums the organism assumed a rough granular appearance. It was nonhemolytic and grew on blood and chocolate agar, but required the V factor for survival on plain mediums. Nitrates were reduced, and glucose was fermented. Agglutination with Fothergill's polyvalent influenza antiserum was positive in a dilution of 1 to 128. The precipitin reaction with the same antiserum was positive in a dilution of 1 to 16. A precipitin test of the organism against the patient's serum elicited a positive reaction in a dilution of 1 to 32. Agglutinations of *Brucella abortus* and *Brucella melitensis*, *H. influenzae* alpha and beta and two parainfluenzae strains with the patient's serum were all negative. The *H. parainfluenzae* was susceptible to 2.5 Oxford units of penicillin per cubic centimeter, or one hundred and twenty-five times as resistant as the standard strain, and to 0.8 unit of streptomycin per cubic centimeter, or four times the resistance of the standard strain. The gram-positive coccus in chains had all the characteristics of *Str. viridans*. It was susceptible to 0.2 unit of penicillin per cubic centimeter, or ten times the resistance of the standard strain, and to 8.0 unit of streptomycin per cubic centimeter, or forty times the resistance of the standard strain. Both organisms were 50 per cent

inhibited by 30 mg. per hundred cubic centimeters of sulfadiazine and not completely inhibited by 100 mg. per hundred cubic centimeters.

*Course.*—The patient was acutely sick on admission; her temperature ranged between 104 and 106 F. for the first two days. Treatment with penicillin was begun on the morning of the third hospital day, before studies of sensitivity had been made, the dosage being 300,000 Oxford units given intramuscularly every three hours. Levels of penicillin in the blood of 8.0 and 10 units per cubic centimeter were obtained fifteen minutes following intramuscular injection; 1.3 and 2.0 units per cubic centimeter were still present three hours following administration of the injection. There was an immediate clinical improvement, but not a complete remission. The temperature persisted up to 101 to 102 F., although blood cultures were sterile.

The level of urea nitrogen in the blood remained normal. The kidney was able to concentrate up to a specific gravity of 1.034. The fasting blood sugar was 95

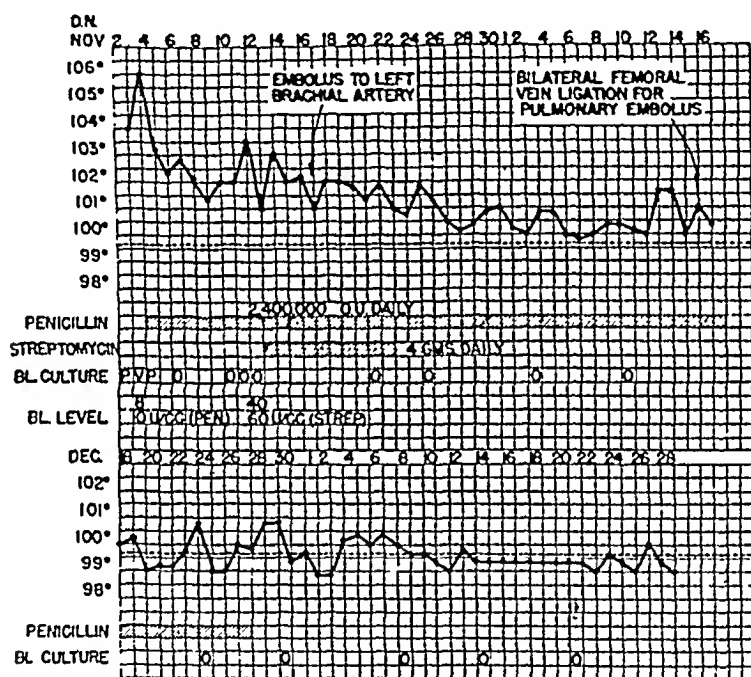


Fig. 3.—Summary of data in case 2.

mg. and the total protein 6.7 Gm. per hundred cubic centimeters. The Kahn reaction was reported to be 3 plus and 2 plus on three different occasions. No macrophages were observed in blood taken from the ear.

Treatment with streptomycin was instituted on September 13, in view of the sensitivity of *H. parainfluenzae* to this drug. One gram every six hours was given intramuscularly for ten days. Levels of streptomycin in the blood ranged from 40 to 60 units per cubic centimeter, and the urine contained up to 1,300 units per cubic centimeter. The temperature was not altered during treatment with streptomycin, but this may have been partly the result of thrombophlebitis subsequent to the lodging of an embolus in the left brachial artery on September 16. The drug itself may provoke a pyrogenic reaction, which subsides after cessation of treatment.

Paresthesia and, finally, numbness appeared in the left hand within twelve hours. Pulsation was not palpable, and the extremity became cold. Intravenous treatment with papavarine, stellate ganglion block and subsequent physical therapy



brought slow improvement. Oscillometric readings were 0.25 units. Horner's syndrome developed on the left side as a result of the ganglion block.

Blood cultures remained sterile, although penicillinase was added to inhibit the effects of the high concentration of penicillin. The temperature dropped to lower levels after a ten day course of streptomycin. The patient continued to improve slowly, the temperature remaining about 100 F. during the fifth week of treatment.

On December 15, the patient noted sudden dyspnea, pleuritic pain on the left side, rapid respiration and tachycardia. The temperature rose to 101 F., and signs of consolidation appeared over the base of the left lung. Roentgenologic examination revealed faint infiltrations in the lower lobe of the right lung and Fleischner's lines in the midportion of the left lung and the lower lobe of the right lung. Tenderness was present in both calves. Both femoral veins were ligated. The femoral vein on the left side was observed to be acutely inflamed and thickened. Dicumaryl was given, and the prothrombin index remained between 35 and 45 per cent for two weeks. There were several subsequent attacks of tenderness in the left calf, with superficial phlebitis over the left ankle, which subsided spontaneously. Because of the persistent rales at the base of the right lung, it was felt that the patient might be experiencing congestive failure, despite normal venous pressure and circulation time. Digitalis was therefore given. Treatment with penicillin was stopped after eight weeks, yet improvement continued. The patient was discharged one month later, on Jan. 29, 1947, and has subsequently been seen in the follow-up clinic. Blood cultures made up to one year following completion of treatment have remained sterile.

*Comment.*—Hunter and Duane,<sup>4</sup> in reviewing the results of antibiotic therapy in subacute bacterial endocarditis caused by gram-negative organisms, have noted conflicting results. They reported 2 cases in which treatment was successful, 1 in which the disease was caused by *H. parainfluenzae* and in which sulfadiazine was used and 1 in which the disease was caused by an unusual gram-negative bacillus and in which sulfadiazine and streptomycin were used. Priest and his co-workers<sup>5</sup> described a case of infection with *H. parainfluenzae* in their series in which good results were achieved by treatment with a combination of penicillin and sulfamerazine, although treatment with each drug alone had failed to sterilize the blood stream. Paul, Bland and White<sup>28</sup> reported the apparent recovery of a patient with endocarditis due to *H. parainfluenzae* following seventeen days of treatment with streptomycin.

Our patient was acutely ill on admission. The early use of antibiotics was probably a life-saving measure. Two organisms were obtained in three successive blood cultures, although both were never grown in the same culture. *H. parainfluenzae* grew in all mediums twice and *Str. viridans* once. In view of the heavy infection (30

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4. Hunter, T. H., and Duane, R. B., Jr.: Subacute Bacterial Endocarditis Due to Gram-Negative Organisms, *J. A. M. A.* **132**:209-211 (Sept. 28) 1946.

5. Priest, W. S.; Smith, J. M., and McGee, C. J.: Penicillin Therapy of Subacute Bacterial Endocarditis, *Arch. Int. Med.* **79**:333-359 (March) 1947.

colonies per cubic centimeter) with the latter organism, it was assumed that *Str. viridans* was probably involved in the valvulitis and was not merely transitory. The sensitivities to antibiotics were of interest. *H. parainfluenzae* was resistant to penicillin, but was moderately sensitive to streptomycin. On the other hand, *Str. viridans* was resistant to streptomycin, but was only moderately sensitive to penicillin. Neither was susceptible to sulfadiazine. Large doses of both penicillin and streptomycin were administered, and high concentrations in the blood were obtained. The level of streptomycin in the blood reached forty times the concentration necessary to inhibit the *parainfluenzae* in vitro. The level of penicillin in the blood reached fifty times the concentration necessary to inhibit the *viridans* in vitro. Obviously, both antibiotics were essential in this case, and, in view of the studies of sensitivity, high dosages were especially necessary.

#### SUMMARY

Two cases of subacute bacterial endocarditis with mixed infection which responded favorably to antibiotic therapy are reported.

In the first case *Corynebacterium pseudodiphthericum* (*hoffmannii*) and *Streptococcus viridans* were present; the former having higher resistance to penicillin than the latter. When the corynebacterium was recognized as one of the infecting agents, penicillin was given in adequate dosage.

In the second case *Str. viridans* and *Hemophilus parainfluenzae* were present. The simultaneous use of two antibiotics was necessary. This represents the third reported case of subacute bacterial endocarditis due to a gram-negative bacillus which was successfully treated with streptomycin.

It is suggested that mixed infection in subacute bacterial endocarditis may be more frequent than is reported. Adequate selection of suitable antibiotics may require identification of all the organisms involved in a given infection.

NOTE: Since this report was submitted, two articles appeared on the use of streptomycin in bacterial endocarditis due to gram-negative bacilli:

Hunter, T. H.: Use of Streptomycin in Treatment of Bacterial Infection, *Am. J. Med.* 2:436-442 (May) 1947.

Massel, B. F.; Zeller, J. W.; Dow, J. W., and Harting, D.: Streptomycin Treatment of Bacterial Endocarditis: Report of a Case, *New England J. Med.* 238:464-466 (April 1) 1948.

Hunter presents 3 cases of endocarditis due to gram-negative bacilli in which the favorable results were attributed at least in part to streptomycin. Massel and others report a case in which the patient recovered after receiving only 13.5 Gm. of streptomycin in six and a half days.

# PRIMARY SYSTEMIC AMYLOIDOSIS SIMULATING CONSTRICTIVE PERICARDITIS

With Steatorrhea and Hyperesthesia

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AMYLOIDOSIS has been divided into the following types: (1) that which is secondary to chronic suppurative diseases, tuberculosis and occasionally rheumatoid arthritis; (2) a type which sometimes accompanies multiple myeloma; (3) a form in which the amyloid is confined to one organ or tissue, and (4) primary systemic amyloidosis. The last-named type is distinctive in that: (1) it is not associated with suppuration, tuberculosis, rheumatoid arthritis or multiple myeloma; (2) it usually does not involve the liver, kidneys, adrenals or spleen to a marked degree; (3) the amyloid is deposited in the heart, lungs, gastrointestinal tract, mucous membranes, skin and striated muscles; (4) the amyloid is capricious in its staining reactions; (5) it often forms nodular amyloid tumors,<sup>1</sup> and (6) patients afflicted with this disease live longer on an average than those with secondary amyloidosis.

This is the fifty-fourth reported case of primary systemic amyloidosis, a case which presents some unusual features of an unusual disease and which until the postmortem examination appeared to be one of constrictive pericarditis.

## REPORT OF A CASE

*History.*—B. I., a 46 year old shoe clerk, was admitted to Billings Hospital on July 18, 1946, complaining of edema of the legs, distention of the abdomen and hypersensitiveness of the skin. He was first seen at this hospital in 1935, complaining of slight "heaviness" in the chest. On roentgen examination a neurofibroma was found in the right posterior portion of the mediastinum. This was removed without incident at another hospital in 1939.

From 1937 to 1944 the patient was treated by desensitization for fall pollen disease, consisting of hay fever, asthma and giant urticaria, which had been present since 1927.

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1. Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis: Involvement of Cardiac Valves, Joints and Bones, with Pathologic Fracture of the Femur, *Arch. Path.* **27**:267 (Feb.) 1939. Steinhaus, F.: Ueber eine seltene Form von Amyloid- und Hyalin-Infiltration am Circulations- und Digestionsapparat, *Ztschr. f. klin. Med.* **45**:375, 1902.

In December 1944 the patient visited the gastrointestinal clinic complaining of anorexia, constipation and gaseous distention of the abdomen. Roentgenograms of the gastrointestinal tract were normal except for a questionable very small duodenal ulcer. Roentgenograms of the chest showed calcified bilateral hilar and left subapical tuberculosis with moderate thickening of the right apical pleura. On a low residue, nonlaxative diet and antispasmodic drugs the patient felt somewhat improved. However, he visited the psychiatry clinic in November 1945, with additional complaints: insomnia, impotence, loss of 30 pounds (13.6 Kg.) in one year and hypersensitivity of the skin to touch and clothing from the neck down. The hypersensitivity was such that the patient wore long underwear twenty-four hours a day to prevent any friction between his skin and his clothes. Associated with the hypersensitivity were "shooting pains" in the lower legs which kept him awake at night, and about which he complained bitterly. An excellent psychiatric explanation for his symptoms was elicited, and the diagnosis was neurotic depression at that time.

In March 1946 the patient began to have edema of the lower extremities, which slowly progressed to involve the sacral area and was accompanied by slight abdominal distention and a mild cough productive of small amounts of sputum, which was occasionally blood streaked.

Laboratory findings had been normal until May 1944, when a urinalysis revealed a slight trace of albumin. A subsequent specimen of urine was normal, but in November 1945, albumin was present (1 plus). On July 5, 1946, there were a few hyaline casts and 0.8 Gm. of albumin per hundred cubic centimeters. The serum albumin at this time was 3.05 Gm. per hundred cubic centimeters and globulin 1.84 Gm. A urea clearance in December 1945 had been 70 by the square root formula. His basal metabolic rate in November 1945 was normal.

*Examination.*—On physical examination, the patient looked chronically ill. There were a few small purpuric spots over the anterior part of the chest just below the clavicles. The eyes were somewhat prominent, but the extraocular movements were normal, and there was no lid lag. The retinal arterioles were generally narrow; the veins were not unusual. The tongue appeared normal. There was no lymphadenopathy. The chest was clear except for signs of fluid at both bases. The heart was not enlarged, the rhythm was regular, and there were no murmurs. The heart sounds were distant. The liver was palpable 5 cm. below the xiphisternum; the edge was smooth and not tender. The abdomen was moderately distended, and shifting dullness was present. Edema of the ankles was marked, it was slight in the thighs, and there was a moderate amount of edema of the sacral area. There was generalized hyperesthesia, most pronounced over the trunk anteriorly and on the volar surfaces of the arms. There was definite loss of pain and temperature sensation over the anterolateral aspect of the lower legs and, to a lesser degree, over the anterior aspect of the thighs. There was some loss of temperature sense in the same areas. Light touch sensation was normal, as was position sense. The patellar reflexes were greatly diminished, and the achilles reflexes were absent.

Studies of the blood showed 3,630,000 to 4,410,000 red blood cells, 12.5 to 13.7 Gm. of hemoglobin, and 5,050 to 8,400 white blood cells, with a differential count of 66 neutrophils, 32 lymphocytes, 2 monocytes and no eosinophils or basophils. The hematocrit value was 43 and the sedimentation rate 4 mm. per hour. Platelet counts were 170,000 and 227,000. Aspiration of the sternum revealed a normal marrow. The specific gravity of the urine was as high as 1.034 with albumin (3 plus) and occasional hyaline casts. The results of the Kahn and Wassermann tests of the blood were negative. Benzidine tests of four stools for

blood gave negative results, and they did not contain parasites or pathogenic organisms. Tubercle bacilli were not found in the sputum on direct examination or on inoculation into guinea pigs. The urea nitrogen and nonprotein nitrogen of the blood were normal until terminally. Urea clearances were 81 and 56 per cent of normal. Total serum lipids were 687 to 757 mg. per hundred cubic centimeters, total serum cholesterol 178 to 220 mg., cholesterol esters 110 to 155 mg. Total plasma proteins varied between 6.03 and 4.36 Gm. per hundred cubic centimeters; the plasma albumin was 3.61 to 2.92 Gm., plasma globulin 2.42 to 1.38 Gm. The lower figures were obtained the day before death. Plasma fibrinogen levels were 0.13, 0.14, and 0.15 Gm. per hundred cubic centimeters. Prothrombin times were 93, 100 and 78 per cent of normal. Serum bilirubin values were normal. Results of two thymol turbidity tests were negative and one plus; of cephalin flocculation tests, one and two plus. A sulfobromophthalein test showed no retention after thirty minutes. A congo red test showed 45 per cent retention by the tissues after sixty minutes; none was excreted in the urine. Bleeding time was four minutes; clotting time twelve minutes (capillary tube method). A tourniquet test for increased capillary fragility gave negative results.

*Treatment and Course.*—After the patient had been hospitalized for a little more than a month, it was found that each day he was passing two or three bulky, soft, grayish stools with a sheen. A three day collection while his food intake was constant, including 100 Gm. of fat per day, showed the stools to be 28 per cent fat, dry weight. Lipid fractions were not studied. Serum calcium content at this time was 4.2 mg. per hundred cubic centimeters. Part of the blood sample was lost, and the serum phosphorus could not be accurately determined; it was approximately 4 mg. per hundred cubic centimeters. After treatment with viosterol (2,640 units of vitamin D per day) and calcium (2.4 Gm. of dicalcium phosphate and 1.6 Gm. of calcium gluconate per day) for two days, the serum calcium was 6.1 mg. per hundred cubic centimeters, and the serum phosphorus 4.6 mg. Values terminally, by which time renal failure had supervened, administration of viosterol and calcium being continued, were calcium 8.2 mg. and phosphorus 9.3. An oral glucose tolerance test was flat, the highest blood glucose value being 93 mg. per hundred cubic centimeters. Lumbar puncture produced clear fluid containing 7 white blood cells and 43 mg. of protein per hundred cubic centimeters. The reaction to the Wassermann test was negative; the colloidal gold curve was 111120000. The Pandy test gave a negative result. The initial pressure was 340 mm.; the final pressure was 260 mm. after 12 cc. had been removed. The dynamics were normal.

Roentgenograms of the chest demonstrated bilateral pleural effusion. The heart was not enlarged. On fluoroscopy, the cardiac pulsations appeared small. No pericardial calcification was seen. Roentgenograms of the gastrointestinal tract were normal except for displacement of the stomach and colon by the enlarged liver. Two electrocardiograms showed small QRS complexes and low T waves. Venous pressures were 18.5, 19.0, and 14.4 cm. of isotonic sodium chloride solution. The arm to tongue circulation time was forty-five seconds.

Because it was felt that the patient probably had constrictive pericarditis, attempts were made to prepare him for pericardiectomy. To this end, he was given infusions of "amigen" and plasma, but because thrombophlebitis of most of the superficial veins of both arms developed, the intravenous therapy had to be interrupted. He was able to take only small portions of the high carbohydrate, high protein, salt-poor diet that was offered him. His response to diuretic drugs was poor. The heart rate was usually 90 to 110.

On the twenty-second day in the hospital, a hemorrhage of the right sclera was noted. On the following day there was a hemorrhage into the left eyelid. At the same time an increase in the number of purpuric spots over the trunk anteriorly occurred. These did not exceed 3 mm. in diameter. On the fifty-ninth day a paracentesis was done, 2,900 cc. of yellow, slightly turbid fluid with a specific gravity of 1.009 and a protein content of 1.91 Gm. per hundred cubic centimeters being removed. Because of the persistent thrombophlebitis, plasma was given intrasternally. On the sixtieth day 1,500 cc. were given by this route. Late that night signs of mild vascular collapse developed. During the next week the blood pressure was only occasionally obtainable, at about 75 systolic and 65 diastolic. The patient became oliguric and progressively more edematous. He died on the sixty-eighth day in the hospital.

*Postmortem Findings.*—The autopsy was begun two and one-half hours after death. It was performed by Dr. J. R. Tobin Jr. and Dr. E. M. Humphreys. The body was that of an emaciated, edematous white man. The tongue and oral mucous membranes appeared normal. There was pitting edema extending from the feet to the axilla. The abdominal cavity contained 3,600 cc. of reddish yellow fluid. There were 1,300 cc. of bloody fluid in pockets between firm fibrous adhesions in the right pleural cavity. The medial surface of the right lung was densely adherent to the mediastinum. The left pleural cavity contained 800 cc. of serous fluid. The right lung weighed 450 Gm., the left 360 Gm. They were firm and subcrepitant. The pleural surfaces were covered with fine fibrous adhesions. There were antemortem thrombi in the radicles of the pulmonary arteries. The pericardial cavity contained 200 cc. of serous fluid. The pericardial surface was opaque and covered with minute yellow-gray granules. The heart weighed 580 Gm. All chambers had thick walls and prominent trabeculae carneae and papillary muscles. The mural endocardium was opaque and studded with yellowish semitranslucent granules. Similar granules were scattered over the cusps of the valves, making them moderately thick and stiff. They were more numerous on the valve leaflets but extended onto the chordae tendineae. All valves were similarly involved. The large coronary arteries were patent. Their intimas were wrinkled and covered with fine semitranslucent granules. This was also true of the intimas of the aorta, pulmonary arteries and venae cavae. The liver appeared small but weighed 1,600 Gm. The capsular surface was opaque and covered with fibrous adhesions. The cut surfaces were of nutmeg appearance, firm and rubbery. The spleen weighed 560 Gm. Its cut surfaces were dry, pink-red and glassy. There was infarction of the cecum and partial infarction of the left kidney. The ileocolic vein was thrombosed. No further abnormalities were found on gross examination of the gastrointestinal tract, kidneys or lymph nodes. The central nervous system was not examined.

By the application of iodine solution and sulfuric acid, amyloid was demonstrated grossly, the substance staining a deep golden brown with iodine and a reddish brown after the addition of acid. It was found in abundance in the myocardium, endocardium and epicardium; the intimas of the aorta and pulmonary arteries; the vessels and connective tissue of the portal triads of the liver; the serosa and blood vessels of the esophagus; the blood vessels of the stomach, intestines and spleen; tunica albuginea of the testes; areolar tissue; serous membranes in general, and in all blood vessels examined. The amyloid also stained with congo red, but the absorption was delayed.

Microscopically, amyloid was seen to be uniformly and selectively deposited in areolar tissue, blood vessels (subintimal and medial deposition), nerves and ganglions and collagenous connective tissue.

There was uniform and massive deposition of amyloid in the myocardium (fig. 1). It seemingly encased fibers, producing widespread atrophic and degenerative changes. It was deposited in small nodules in the endocardium of the ventricles and valves. The epicardial fat, vessels and nerves were similarly involved.

There was evidence of an old tuberculous process in one section of the right lung and in the apex of the left, but there was no evidence of active tuberculosis. There were thick hyaline calcified nodules in the right lung and a hyaline apical scar in the left. Amyloid was deposited in the septums of the lung, hyaline scars and alveolar walls, as well as in blood vessels.

There was massive amyloidosis of the spleen. Foreign body giant cells were present about the amyloid infiltrates.

The following organs contained moderate amounts of amyloid tissue: the adrenals; the entire gastrointestinal tract from esophagus to anus, chiefly in the muscularis mucosae and muscular coat, but also in the villi; and the kidneys, the amyloid being in the glomerular tufts, and, to a lesser degree, in the tubules.

There was heavy and uniform deposition of amyloid in the nerve trunks and perineural connective tissue at the root of the mesentery and in the celiac plexus (fig. 2). All recognizable ganglions contained amyloid.

It was also deposited about nerves, blood vessels and connective tissue of the liver, pancreas (which was also the site of intralobular fibrosis and acinar atrophy), thyroid, urinary bladder, prostate, seminal vesicles, tunica albuginea of the testes, skin, tongue and buccal mucous membranes.

There were small amounts in skeletal muscle fibers, the greatest amount being in their tendinous connections.

Amyloid was not found in the bone marrow; the maturation of blood elements was normal.

#### COMMENT

When amyloid is deposited in the tongue, skin or lymph nodes in such a manner as to produce gross changes, the diagnosis should be readily established by biopsy. Enlargement of the tongue has been noted in 20 patients with this disease and was an important presenting complaint in 16 of them in whom the enlargement was so marked that dysarthria with or without dysphagia was present.<sup>2</sup> Amyloid deposits have been observed grossly in the skin of 11 patients with primary systemic amyloidosis. They have produced lesions described as sclerodermic,<sup>3</sup> papular, eczematous,<sup>4</sup> opalescent, firm and nodular.<sup>5</sup> Enlarge-

2. Eisen, H. N.: Primary Systemic Amyloidosis, *Am. J. Med.* **1**:144 (Aug.) 1946.

3. (a) Lubarsch, O.: Zur Kenntnis ungewöhnlicher, Amyloidablagerungen, *Virchows Arch. f. path. Anat.* **271**:867 (March 20) 1929. (b) Gerstel, G.: Ueber atypische Lokalisation des Amyloids insbesondere über die Makroglossia amyloides diffusa, *ibid.* **283**:466 (Feb. 5) 1932. (c) Gaupp, A.: Ein Fall von generalisierter, atypischer Amyloidose (Paramyloidose), *Düsseldorf, G. H. Nolte*, 1934.

4. Lindsay, S., and Knorp, W. F.: Primary Systemic Amyloidosis, *Arch. Path.* **39**:315 (May) 1945.

5. Mollow, W., and Lebell, H.: Zur Klinik der systematisierten Amyloidablagerung, *Wien. Arch. f. inn. Med.* **22**:205, 1932.

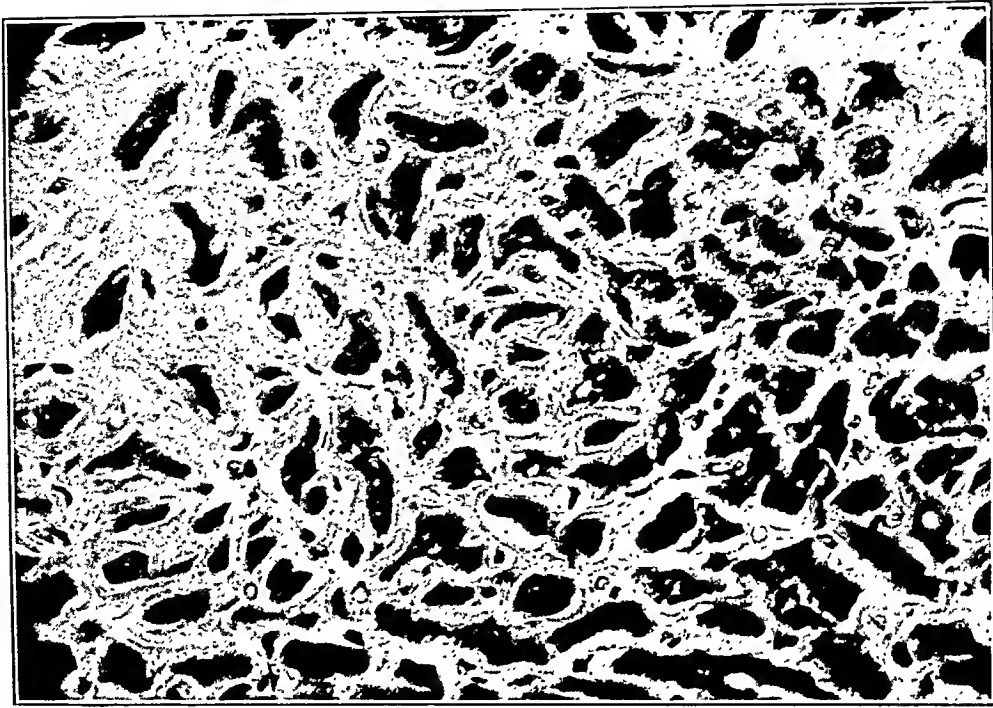


Fig. 1.—Heart; hematoxylin and eosin stain. The interstitium consists chiefly of amyloid, which encases fibers and is associated with atrophy and degeneration, but not with necrosis.  $\times 292$ .

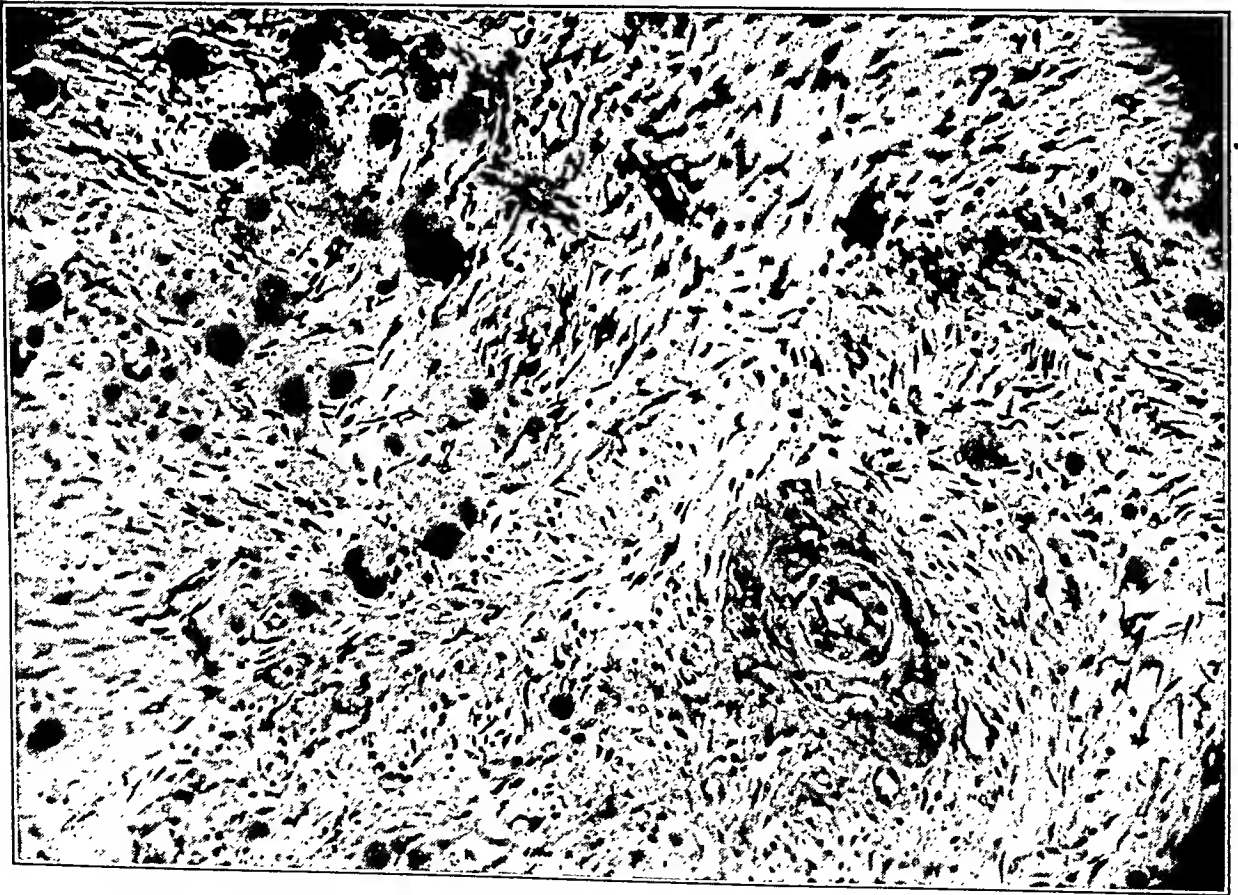


Fig. 2.—Celiac ganglions; hematoxylin and eosin stain. Amyloid surrounds the blood vessel to the right of and below the center. It is also deposited indiscriminately throughout the slide, appearing as poorly defined masses and sharply defined, roughly circular darker areas.  $\times 138$ .



ment of lymph nodes has been reported generalized and localized in the form of amyloid tumors.<sup>4</sup>

Unless these external changes are present, the diagnosis is apt to be difficult. The congo red test has been done in 12 of the reported cases and was equivocal or negative in 6 of them. Involvement of skeletal muscle has been noted in 19 cases. Thus, a specimen of a muscle for biopsy may be diagnostic if the possibility of this disease is entertained. Such a procedure would have established the nature of the illness in the reported case.

Dirske<sup>6</sup> has recently discussed the roentgen findings in the chest reported in primary systemic amyloidosis and suggests that further observations may show them to be of some diagnostic value when the disease happens to involve the mediastinum and lungs.

The combination of elevated venous pressure, prolonged circulation time, low pulse pressure, small cardiac movements on fluoroscopy, low electrocardiographic voltage, hepatomegaly, decreased serum albumin with a normal concentration of globulin, albuminuria, dependent edema and ascites led to a diagnosis of constrictive pericarditis. The bizarre generalized hypersensitivity of the skin to touch was believed to be due in part to a peripheral neuropathy and in part a neurotic manifestation. The low plasma fibrinogen and prolonged bleeding time were not satisfactorily explained. Steatorrhea has been observed in constrictive pericarditis<sup>7</sup> and also in amyloidosis.<sup>8</sup>

It is not surprising that deposition of amyloid in the heart should simulate constrictive pericarditis. In both diseases the normal contraction and relaxation of the chambers is precluded, in the one disease by confinement of the individual muscle fibers and in the other by confinement of the organ as a whole. However, in none of the previously reported cases was constrictive pericarditis diagnosed, and in only a small proportion of the cases were the findings suggestive of this disease. Fifty-two per cent (28) of the patients had edema; 30 per cent (16) had hydrothorax; 28 per cent (15) had ascites. In addition to the reported case, one venous pressure (3) and no circulation times or appearances of cardiac action of fluoroscopy are recorded. Since Lindsay's survey<sup>9</sup> of 45 cases of primary systemic amyloidosis, which included

6. Dirske, P. R.: Primary Amyloidosis of the Lungs, *Am. J. Roentgenol.* **56**:577 (Nov.) 1946.

7. Clemmesen, J.: Steatorrhea Arthro-Pericarditica (Mesenteric Chyladenectasis): Review and Report of a Case, *Acta med. Scandinav.* **121**:495, 1945.

8. Schein, J.: Syndrome of Non Tropical Sprue with Hitherto Undescribed Lesions of the Intestine, *Gastroenterology* **8**:438 (April) 1947. Adlersberg, D., and Schein, J.: Clinical and Pathologic Studies in Sprue, *J. A. M. A.* **154**:1459 (Aug. 23) 1947.

9. Lindsay, S.: The Heart in Primary Systemic Amyloidosis, *Am. Heart J.* **32**:419 (Oct.) 1946.

electrocardiograms in 12 cases, 6 of these showing low voltage, 9 additional cases have been reported.<sup>10</sup> Electrocardiograms were made in all of these, and 7 showed low voltage. Thus, of the total of 21 electrocardiograms which have been reported, 13 have shown low voltage.

One of the most interesting and unusual features of this case was the spectacular involvement of the nerves with the attendant symptoms. Similarly distributed deposits have been reported by DeNavesquez and Treble<sup>10b</sup> and by Götze and Krücke.<sup>11</sup> These patients complained of muscular weakness, paralyses, incontinence, impotence, paresthesias and various other neurologic disturbances. Ganglions and peripheral nerves were strikingly involved in both cases, and the patient of Götze and Krücke also had extensive deposits in blood vessel walls throughout the brain substance.

Purpura has been seen in 10 cases. It has been attributed to amyloid deposition in cutaneous blood vessels,<sup>1</sup> but, as has been remarked by Eisen,<sup>2</sup> this explanation is not satisfactory, for perivascular hemorrhages do not occur elsewhere. In any event, it is difficult to understand why the skin should be involved exclusively. Epistaxis and bleeding ulcers of the skin have been found.<sup>4</sup> The plasma fibrinogen in the reported case was not low enough to produce hemorrhagic manifestations per se, although it is perhaps conceivable that it in combination with increased venous pressure and low serum calcium was instrumental. No abnormalities of the clotting mechanism have been reported previously. Massive gastrointestinal bleeding has been described,<sup>12</sup> but this was apparently due to changes in the mucosa rather than changes in the blood.

It is stated in the protocol of one of these cases,<sup>12b</sup> in which there was marked amyloidosis of the gastrointestinal tract, that the patient "had frequent foul-smelling light yellow stools . . ." As in the subject of the present report, steatorrhea may have been present.

Two cases of amyloidosis involving the small intestine have recently been reported.<sup>8</sup> It has been suggested that amyloid disease may be

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10. (a) Eisen.<sup>2</sup> (b) De Navesquez, S., and Treble, H. A.: Case of Primary Generalized Amyloid Disease with Involvement of Nerves, *Brain* **61**:116 (March) 1938. (c) Soisalo, P., and Ritama, V.: Atypical Amyloidosis with Special Consideration of Heart, *Acta med. Scandinav.* **116**:260, 1944. (d) Orloff, J., and Felder, L.: Primary Systemic Amyloidosis: Jaundice as a Rare Accompaniment, *Am. J. M. Sc.* **212**:275 (Sept.) 1946. (e) Atkinson, A. J.: Clinical Pathological Conference, *Gastroenterology* **7**:477 (Oct.) 1946. (f) Zemp, F. E.: Primary Amyloidosis, *Ann. Int. Med.* **26**:448 (March) 1947.

11. Götze, W., and Krücke, W.: Ueber Paramyloidose mit besonderer Beteiligung der peripheren Nerven und granulärer Atrophie des Gehirns, *Arch. f. Psychiat.* **114**:183 (Nov. 7) 1941.

12. (a) Lubarsch.<sup>8a</sup> (b) Golden, A.: Primary Systemic Amyloidosis of the Alimentary Tract, *Arch. Int. Med.* **75**:413 (June) 1945.

found to be an important cause of the sprue syndrome if the intestinal tracts of such patients are examined with this in mind.

This patient lived about two years after the onset of his symptoms, a somewhat shorter period than the average of thirty-two months found by Eisen.<sup>2</sup>

There is some reason to associate amyloidosis with an abnormality of one or more of the serum globulins. Reimann, Koucky and Eklund<sup>13</sup> gave 4 rabbits approximately ninety-three intramuscular injections of sodium caseinate over a period of eight to thirteen months. During this time the amount of blood globulin was increased from two to four times over the normal level. Each of the animals died from extensive amyloid disease. Kuczynski<sup>14</sup> produced amyloid disease in mice simply by feeding large amounts of casein. Dick and Leiter<sup>15</sup> noted hyperglobulinemia in association with the amyloidosis produced in rabbits by the use of various strains of streptococci. Reimann and Eklund have noted that the secondary form of amyloidosis occurs in diseases in which hyperglobulinemia is frequently present. They report a case<sup>16</sup> in which forty-one injections of bacterial vaccine were given at more or less regular intervals over a period of twenty-two months. Post-mortem examination revealed extensive amyloidosis of the spleen, liver, kidneys and adrenals. Their patient also had chronic arthritis, which may have been an important factor in the cause. Shortly after death the blood proteins were 4.7 Gm. per hundred cubic centimeters, composed of 1.29 Gm. fibrinogen, 2.67 Gm. globulin and 0.74 Gm. albumin. Serum globulins have been noted to fall rather strikingly in patients with multiple myeloma when amyloidosis developed.<sup>17</sup> Our patient's serum globulin fell very late in the course; it is difficult to attach much significance to this. This patient had pollen vaccine therapy for fall pollen disease, but large numbers of patients receive similar therapy without development of amyloidosis. No history of allergy was encountered by Eisen in his collection of 48 cases.<sup>2</sup>

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13. Reimann, H. A.; Koucky, R. F., and Eklund, C. M.: Primary Amyloidosis Limited to Tissues of Mesodermal Origin, *Am. J. Path.* **11**:977 (Nov.) 1935.

14. Kuczynski, M. H.: Edwin Goldmanns Untersuchungen über cellulare Vorgänge im Gefolge des Verdauungsprozesses auf Grund nachgelassener Präparate dargestellt und durch neue Versuche ergänzt, *Virchows Arch. f. path. Anat.* **239**: 185, 1922.

15. Dick, G. F., and Leiter, L.: Experimental Amyloidosis and Hyperglobulinemia, *Tr. A. M. Physicians* **52**:246, 1937.

16. Reimann, H. A., and Eklund, C. M.: Long Continued Vaccine Therapy as a Cause of Amyloidosis, *Am. J. M. Sc.* **190**:88 (July) 1935.

17. Tarr, L., and Ferris, H. W.: Multiple Myeloma Associated with Nodular Deposits of Amyloid in Muscles and in Joints, *Arch. Int. Med.* **64**:820 (Oct.) 1939. Chester, W.: Multiples Myelom und Hypoproteinämie, *Ztschr. f. klin. Med.* **124**: 466, 1933. Freeman, I., and Krause, L. A. M.: Multiple Myeloma with Localized Amyloid Deposits, *Bull. School M. Univ. Maryland* **26**:7 (Oct.) 1941.

## SUMMARY

A case of primary systemic amyloidosis is presented. Interesting features of the case include its clinical resemblance to constrictive pericarditis, the occurrence of steatorrhea, hypocalcemia, a tendency to bleed and the presence of neural involvement by the amyloid substance.

The diagnosis is difficult in the absence of a positive congo red test or certain common external manifestations, such as involvement of the skin, lymph nodes or tongue; it was not made before death in this case. Biopsy of muscle might have made the diagnosis possible.

The combination of elevated venous pressure, low pulse pressure, small cardiac movements, low electrocardiographic voltage, hepatomegaly, low serum albumin with normal globulin, albuminuria, dependent edema and ascites led to a diagnosis of constrictive pericarditis. Most of these findings have been noted in primary amyloidosis before. Cardiac inactivity and prolonged circulation time have not been previously reported. Elevation of venous pressure has been noted once.

The occurrence of steatorrhea and hypocalcemia is of interest in connection with a recent suggestion that amyloidosis may occasionally cause the sprue syndrome.

Unexplained bleeding was present and has been noted in other cases.

While neural involvement has been reported twice, neither patient had the exquisite cutaneous hypersensitivity found in this case.

## STUDIES ON HYPERTENSION

### VII. Mechanism of the Fall in Arterial Pressure Produced by High Spinal Anesthesia in Patients with Essential Hypertension

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AND

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HIGH spinal anesthesia was employed in previous studies<sup>1</sup> to lower the blood pressure of patients with essential hypertension. From these studies certain information and conclusions have been drawn regarding the probability that the drop in blood pressure is due to interruption of vasomotor function.

The work of Smith and his associates<sup>2</sup> and Rovenstine and his associates<sup>3</sup> suggested that the fall in blood pressure due to spinal

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1. Gregory, R.; Lindley, E. L., and Levine, H.: Studies on Hypertension: I. The Effect on the Renal Function of Decreasing the Blood Pressure of Patients with Hypertension, *Tex. Rep. Biol. & Med.* **1**:59-76, 1943; II. The Effect of Spinal Anesthesia on the Blood Pressure of Hypertensive Patients: Its Possible Bearing on the Pathogenesis of Essential Hypertension, *ibid.* **1**:167-206, 1943. Gregory, R.; Levine H., and Lindley, E. L.: Studies on Hypertension: III. The Site of Action of Angiotonin; the Pressor Effects of Angiotonin on Patients Having Essential Hypertension, and Possible Relationship to the Pathogenesis of Essential Hypertension, *ibid.* **2**:121-134, 1944. Gregory, R.; Ewing, P. L.; Levin, W. C., and Ross, G. T.: Studies on Hypertension: IV. Bioassay of Vasoconstrictor Substances in Ultrafiltrates of Citrated Blood Plasma from Patients with Normal Blood Pressures, Patients with Essential Hypertension and Patients Made Hypertensive by Intravenous Injections of Angiotonin (Hypertension), *Arch. Int. Med.* **76**:11-21 (July) 1945. Gregory R., and Levin, W. C.: Studies on Hypertension: V. Effect of High Spinal Anesthesia on the Blood Pressure of Patients with Hypertension and Far-Advanced Renal Disease—Its Possible Relationship to the Pathogenesis of Hypertension, *J. Lab. & Clin. Med.* **30**:1037-1043, 1945. Gregory, R.; Levin, W. C.; Ross, G. T., and Bennett, A.: Studies on Hypertension: VI. Effect of Lowering the Blood Pressure of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearances, *Arch. Int. Med.* **77**:385-392 (April) 1946.

2. Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chasis, H., and Ranges, H. A.: The Effect of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arteriolar, and Especially Those of the Renal Circulation, *J. Clin. Investigation* **18**:319-341, 1939.

3. Rovenstine, E. A.; Papper, E. M., and Bradley, S. E.: Circulatory Adjustments During Spinal Anesthesia in Normal Man with Special Reference to the Autonomy of Arteriolar Tone, *Anesthesiology* **3**:421-428, 1942.

anesthesia is due to decreased cardiac output resulting from decreased venous pressure and diminished venous return to the heart. In view of the fact that both of these studies were done on subjects with normal blood pressure, it appears necessary that these observations be applied to patients with essential hypertension. It is conceivable that the role played by the vasomotor apparatus in maintaining normal blood pressure may be different from the role of this mechanism in maintaining elevations of arterial pressure in hypertension.

In the previous studies <sup>4</sup> no observations were made on venous pressures. The present study is the first of several devised to elucidate the mechanism of the fall of arterial pressure produced by spinal anesthesia in patients with essential hypertension.

The mechanism of the fall of arterial pressure during spinal anesthesia has engaged the attention of a number of workers. In general, the studies have been concerned with whether there is a decrease in cardiac output, and, if so, whether this is causally related to the fall in arterial pressure.

Burch and Harrison <sup>5</sup> studied the effect of spinal anesthesia on the cardiac output of dogs. They showed that the fall in arterial pressure produced the fall in cardiac output in some instances, and in most instances the degree of fall in arterial pressure was disproportionately greater than the fall in cardiac output. They concluded that the initial change is in the arterial pressure and that the venous return and cardiac output are affected secondarily.

Ferguson and North <sup>6</sup> have emphasized, in a study on dogs, the slight role that splanchnic dilatation plays in the fall of arterial pressure during spinal anesthesia. But they have further demonstrated the essential part played by the general vasomotor paralysis in the fall of arterial pressure induced by spinal anesthesia.

By plethysmographic studies on a finger and a toe, Neumann, Foster and Rovenstine <sup>7</sup> have stressed the importance of compensating vasoconstriction in unanesthetized areas in the maintenance of blood pressure during spinal anesthesia.

Sarnoff and Arrowood <sup>8</sup> have made an important contribution to the understanding of the effects of spinal anesthesia on blood pressure.

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4. Smith and others.<sup>2</sup> Rovenstine, Papper and Bradley.<sup>3</sup>

5. Burch, J. C., and Harrison, T. R.: The Effect of Spinal Anesthesia on the Cardiac Output, *Arch. Surg.* **21**:330-332 (Aug.) 1930.

6. Ferguson, L. K., and North, J. P.: Observations on Experimental Spinal Anesthesia, *Surg., Gynec. & Obst.* **54**:621-634, 1932.

7. Neumann, C.; Foster, A. D., Jr., and Rovenstine, E. A.: The Importance of Compensating Vasoconstriction in Unanesthetized Areas in the Maintenance of Blood Pressure During Spinal Anesthesia, *J. Clin. Investigation* **24**:345-351, 1945.

8. Sarnoff, S. J., and Arrowood, J. G.: Differential Spinal Block, *Surgery* **20**:150-159, 1946.

They have shown that "differential spinal block" with low concentrations of procaine hydrochloride in patients with normal blood pressure may produce significant falls in arterial pressure in spite of an absence of paralysis of skeletal muscle. From the lack of paralysis of skeletal muscle, they have concluded that there was no decrease in venous return and, consequently, no decrease in cardiac output.

#### METHOD OF STUDY

The venous and arterial pressures were simultaneously recorded at one-half to two minute intervals before, during and following recovery from high spinal anesthesia. The technic of spinal anesthesia was that employed in our previous studies. Anesthesia uniformly reached the level of the fourth dorsal segment or higher—in most instances it was higher. These observations have been made in 5 patients with normal arterial pressures and twelve times in 10 patients with essential hypertension.

Simultaneous observations of arterial and venous pressures were made because it was thought that the time relationships between the changes in these values would be of some importance in arriving at conclusions regarding cause and effect relationships.

Arterial pressures were determined in the usual way with the cuff and mercury manometer. Venous pressures were measured with a water manometer, using 2.5 per cent of sodium citrate in isotonic solution of sodium chloride in the system. The needle was allowed to remain continuously in one of the antecubital veins. Precaution was always exercised to ascertain that the liquid in the water manometer registered respiratory oscillations.

Spinal puncture was accomplished in the conventional lateral recumbent position, with a malleable needle. The patient was then placed in the dorsal recumbent position. The position of the arm in which observations of venous pressures were made was fixed and its position to the axillary midline established so that the level of the vein and this line were the same, or, if different, the difference was recorded. After adequate control observations were made in this position, 150 mg. of procaine hydrochloride in 3 cc. of spinal fluid was rapidly injected intrathecally.

#### RESULTS.

Five patients with normal blood pressure were studied. Figure 1 (H. M.) demonstrates that the arterial pressure may fall before the venous pressure falls. The systolic pressure had fallen from 110 mm. of mercury to 94 mm. of mercury, while the venous pressure was above the control level. The recovery of both systolic pressure and venous pressure began about the same time. But the slope of the curve of the systolic blood pressure indicates a slightly more rapid recovery compared with the curve of venous pressure. It is important to note also that the diastolic pressure showed a significant drop from 64 to 52 mm. of mercury. We believe that this indicates a vasomotor influence in maintaining arteriolar tone even in patients with normal blood pressure. This is at variance with the work of Rovenstine, Papper and Bradley.<sup>3</sup>

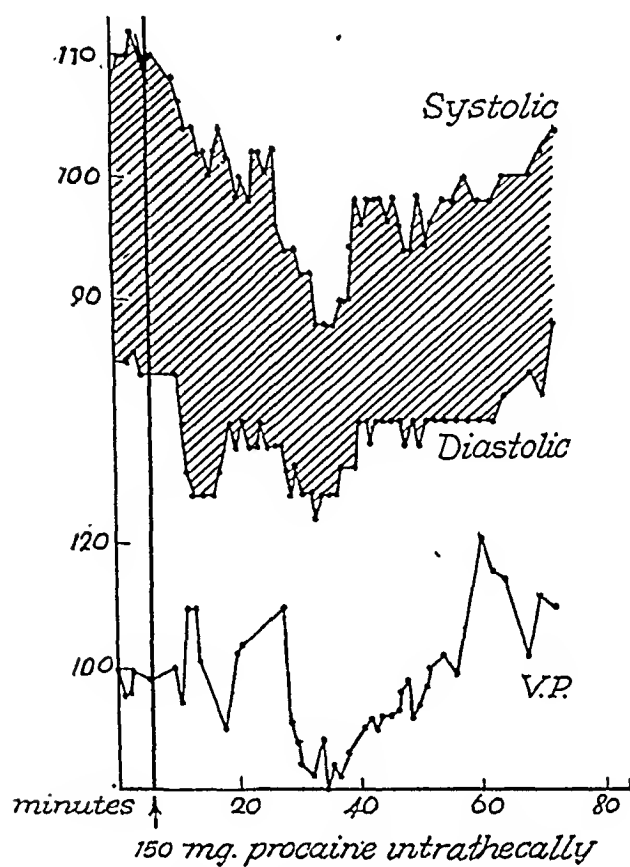


Fig. 1.—Graph of levels of blood pressure of patient H. M., demonstrating that arterial pressure may fall before the venous pressure falls.

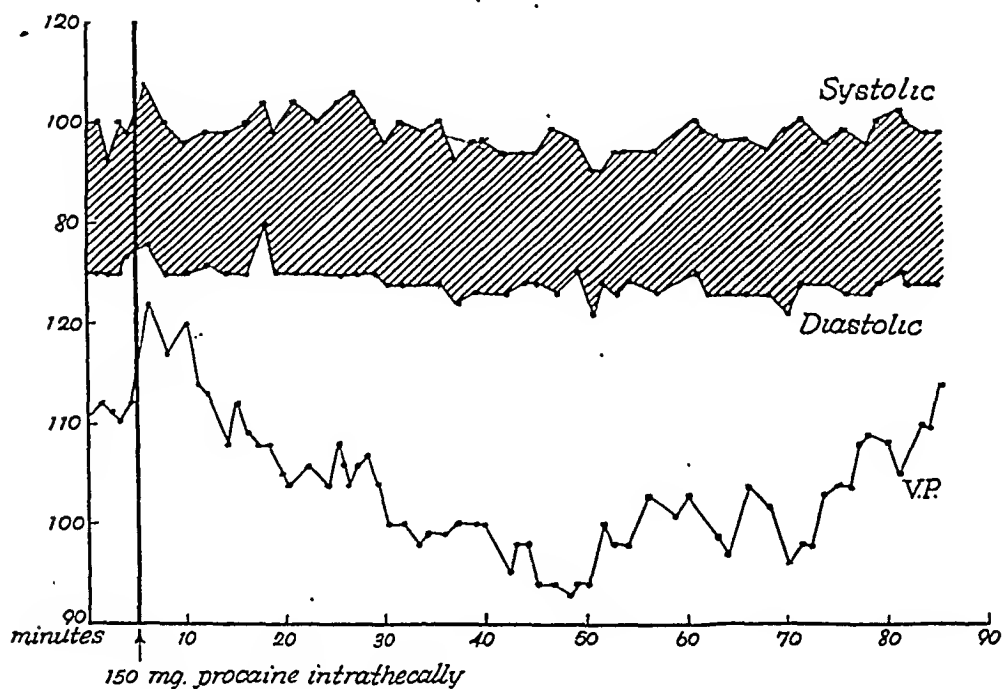


Fig. 2.—Graph of levels of blood pressure of patient L. D. K., demonstrating that venous blood pressure may fall significantly with no fall in arterial pressure.



We further believe that the fall in systolic pressure which preceded the fall in venous pressure makes it likely that the fall in arterial pressure is not due to decrease in cardiac output.

Figure 2 (L. D. K.) shows a decided decrease in venous blood pressure twenty minutes before any decrease in systolic blood pressure, which was slightly, if any, below preanesthetic levels. The diastolic pressure hardly fell at all. The results in this patient show that the venous pressure may fall significantly with no fall in arterial pressure.

Figure 3 (A. H.) also demonstrates that the venous pressure may fall an appreciable amount without any sustained fall in either systolic or diastolic pressures.

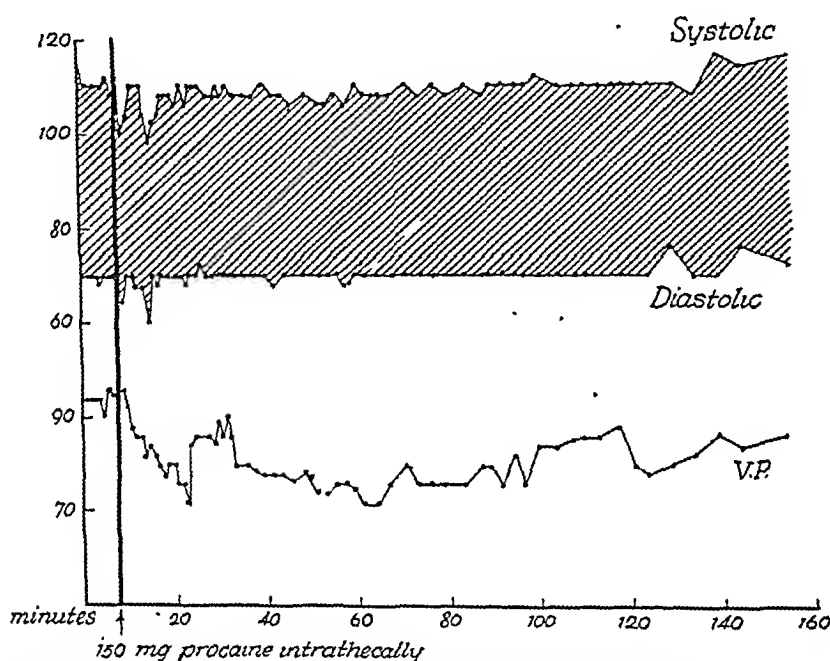


Fig. 3.—Graph of levels of blood pressure of patient A. H., demonstrating fall in venous pressure without any sustained fall in arterial pressure.

Figure 4 (J. T. J.) illustrates that the fall in venous pressure may precede the fall in systolic pressure but that the systolic pressure may continue to fall in spite of a progressive rise in the venous pressure. The diastolic pressure also shows a distinct and sustained fall coinciding with the period of greatest fall in systolic pressure.

Figure 5 (L. Y.) also demonstrates that the venous pressure fell before the arterial pressure and that the diastolic pressure fell during spinal anesthesia.

The limited number of 5 cases studied indicates that there is no constant time relationship between the falls in venous and arterial pressures produced by spinal anesthesia in patients with normal blood pressure. The venous pressure may fall first, or the arterial pressure may fall first.

It should be also noted that a fall in venous pressure is not necessarily associated with a fall in arterial pressure. Significantly, 3 of the normal persons showed falls in diastolic blood pressure. This point emphasizes

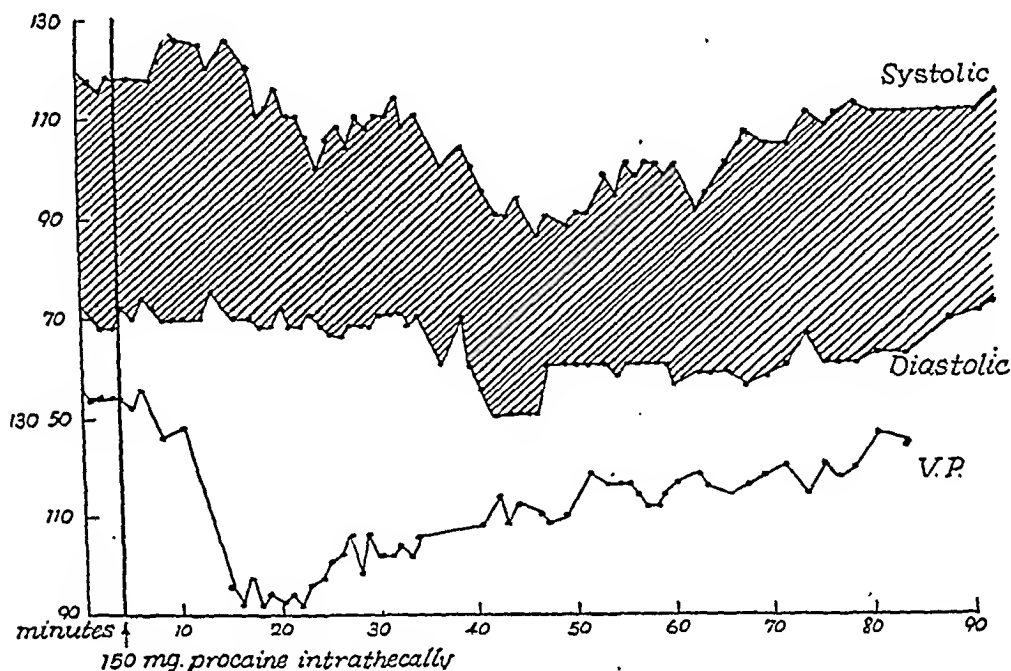


Fig. 4.—Graph of levels of blood pressure of patient J. T. J., showing a fall in venous pressure preceding the fall in systolic pressure.

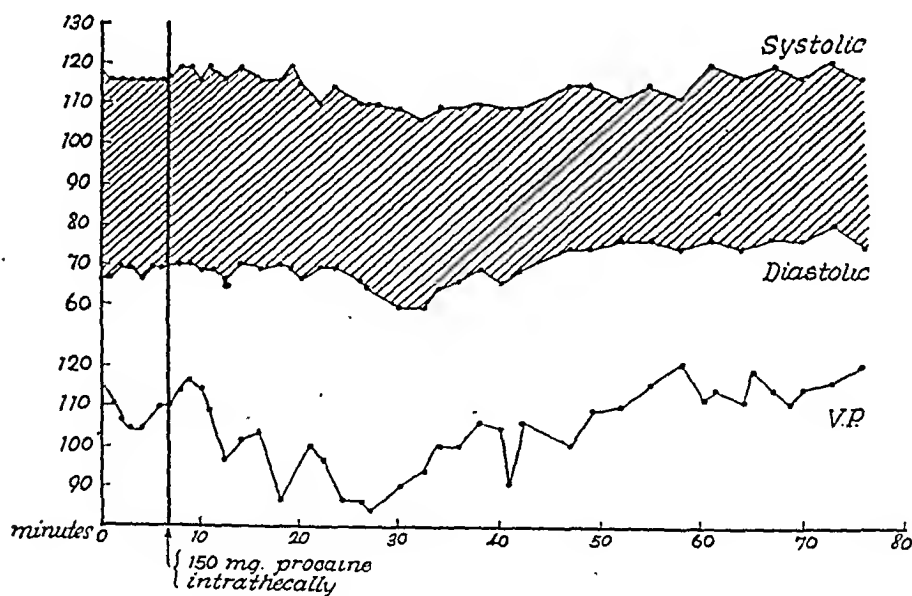


Fig. 5 (L. Y.).—Fall in venous pressure preceding the fall in arterial pressure.

the importance of the role that vasomotor function plays in maintaining normal arteriolar tonus.

According to the results, patients with hypertension may be divided into three groups: (a) those that showed a drop in venous pressure first with no significant drop in arterial pressure (two studies on 1

patient), (b) those showing a drop in arterial pressure first (7 patients) and (c) those showing a drop in venous pressure first, with a subsequent drop in arterial pressure (2 patients).

*Patients Showing First a Drop in Venous Pressure Without a Significant Drop in Arterial Pressure.*—This was shown to be the case in only 1 patient. Because no significant fall in arterial pressure occurred, the determination was repeated, with similar results. Figure 6, which is a graph of the first study on patient K, shows a fall in venous pressure

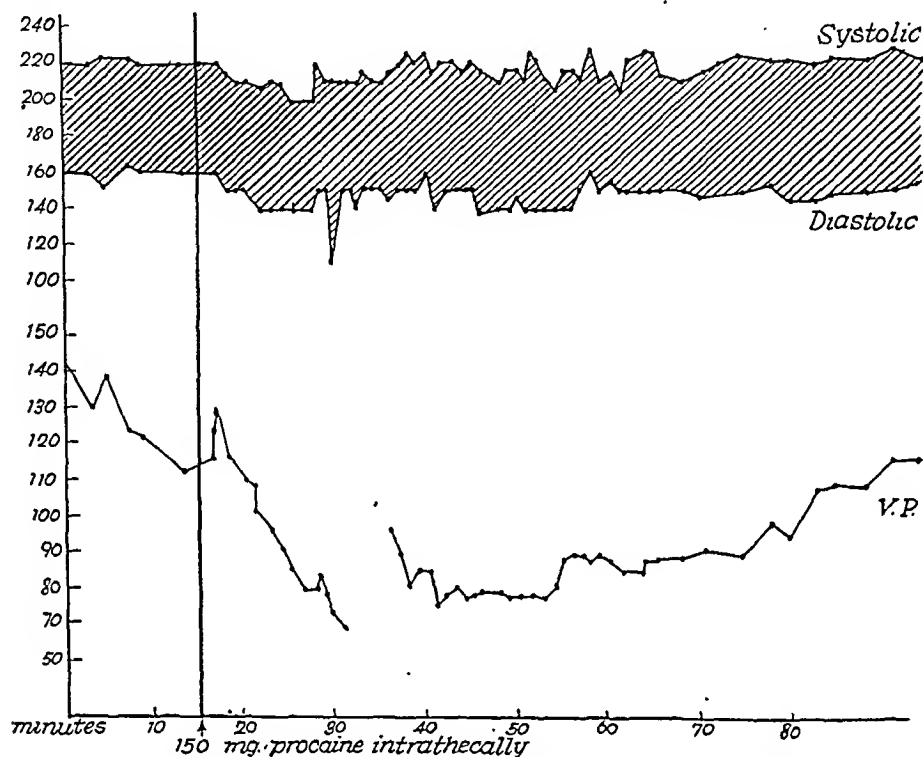


Fig. 6.—Graph of levels of blood pressure in patient K.

from a control level of about 115 mm. of isotonic solution of sodium chloride to 70 mm. and a sustained fall to 80 mm. of isotonic solution of sodium chloride. There was a slight fall in arterial pressure, which quickly returned to control levels while the venous pressure remained at the lowest level of the sustained fall. Figure 7 (patient K) shows practically identical results.

Although the falls in systolic and diastolic pressures were slight in both of these studies on patient K, we emphasize that there was a fall in diastolic as well as systolic pressure. In figure 7, the fall that occurred in systolic and diastolic pressure, about forty minutes after the induction of spinal anesthesia, was probably the result of casual change due to prolonged rest rather than to the spinal anesthesia.

*Patients Showing Falls in Arterial Pressure Before Falls in Venous Pressure.*—Figures 8 through 11 graphically present the data on 4

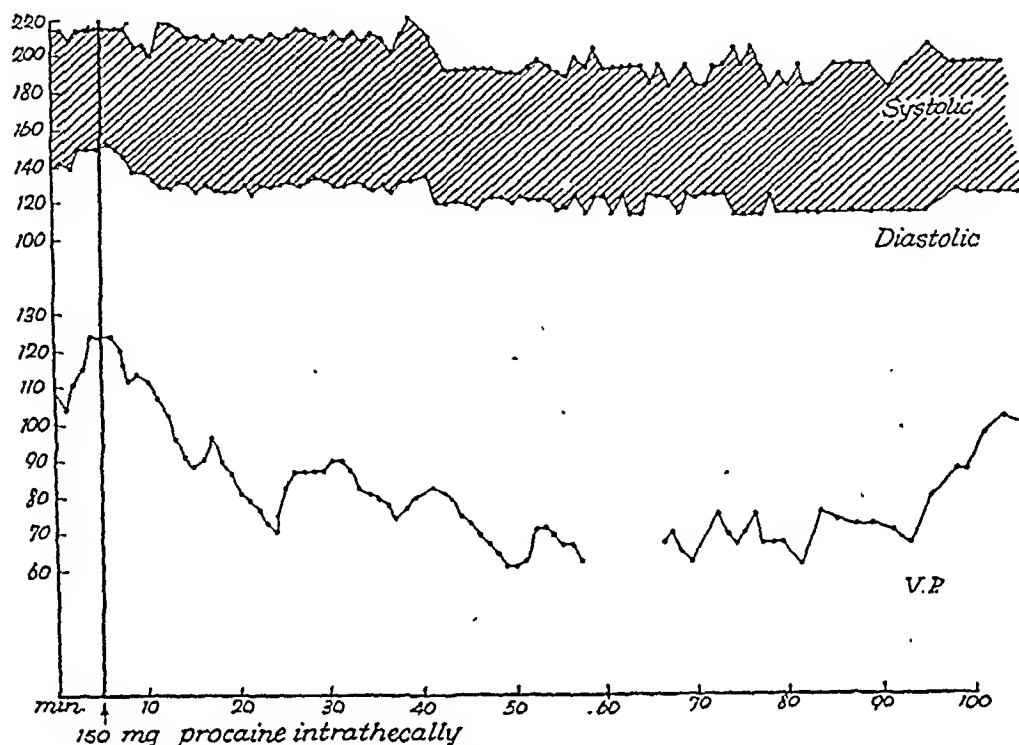


Fig. 7.—Graph of levels of blood pressure in patient K.

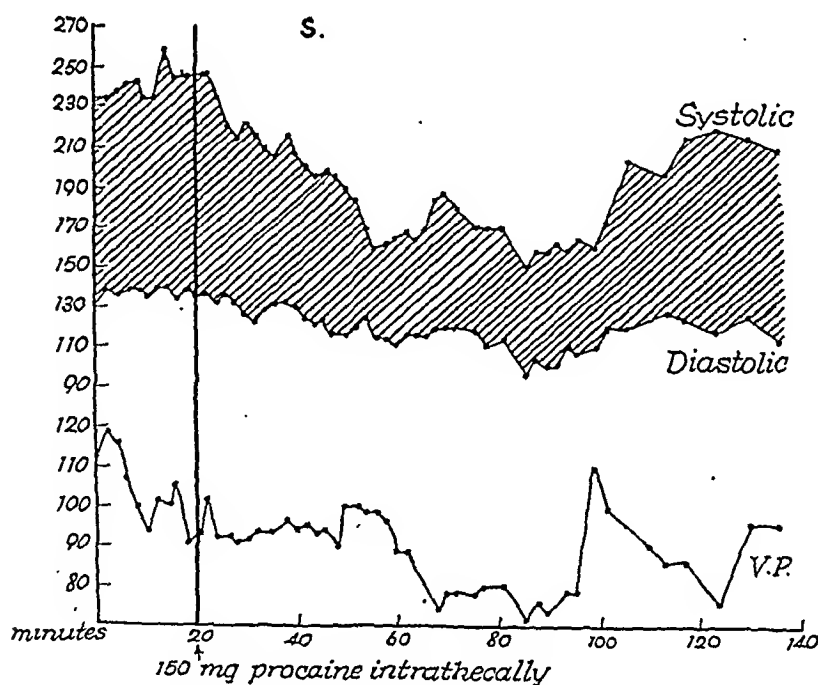


Fig. 8.—Graph of levels of blood pressure in patient S.

patients in whom the arterial pressure fell significantly before there was an appreciable drop in venous pressure.

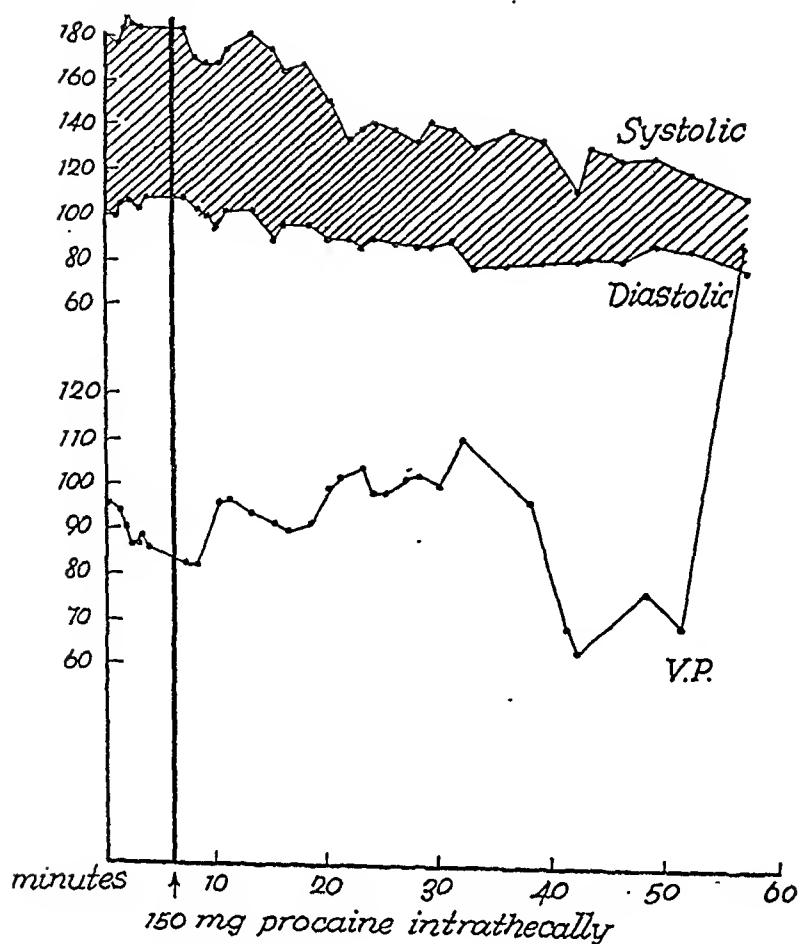


Fig. 9.—Graph of levels of blood pressure in patient J. L.

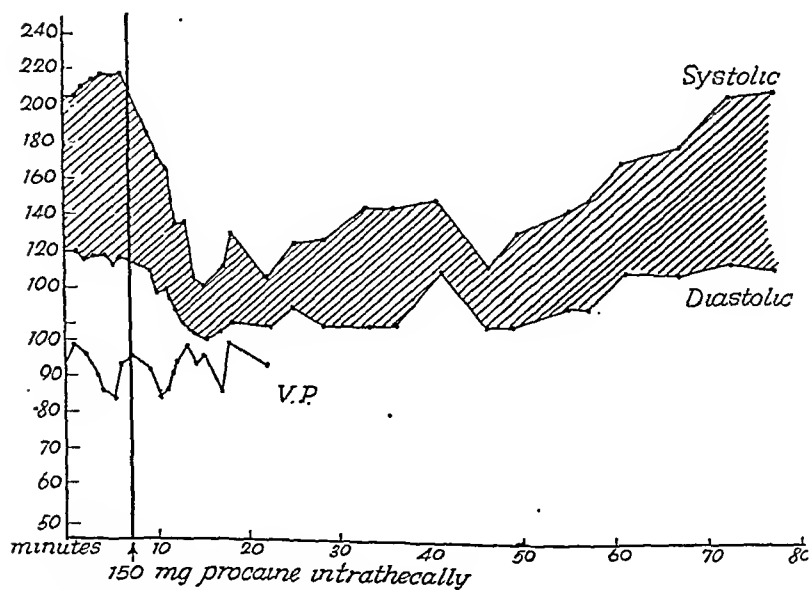


Fig. 10.—Graph of levels of blood pressure in patient B. J.

As in the previous group of patients, we feel that it is highly significant that there was a moderate or decided fall in the diastolic pressure. In a group of 7 patients the diastolic pressure dropped to

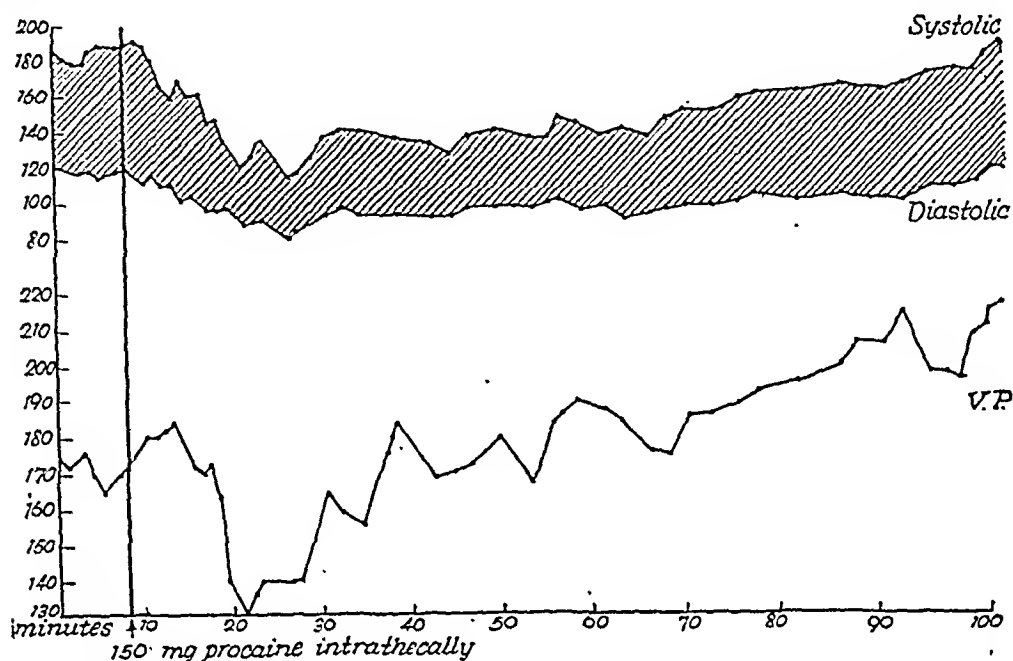


Fig. 11.—Graph of levels of blood pressure in patient H. M. C.

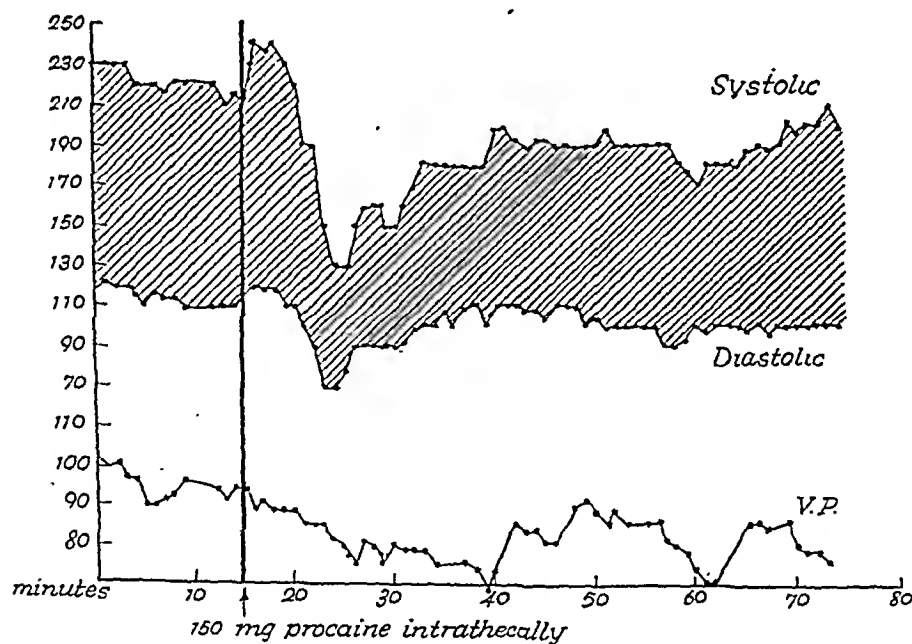


Fig. 12.—Graph of levels of blood pressure in patient D.

normal level in 5. The remaining 2 patients showed decided falls in diastolic pressure, but not to normal levels.

*Falls in Venous Pressure Before Arterial Pressure.*—There are only 2 patients who showed results which can be classified in this group.

The results on patient D (fig. 12) have been classified in this category, but the results are equivocal. While it is true that the venous pressure had begun to fall before the arterial pressure, both the systolic and the diastolic pressures fell to their lowest points before the venous pressure fell to its lowest level. It is also to be emphasized that the arterial pressure was rising while the venous pressure was falling. The venous pressure rose to control levels, while a significant drop in the arterial pressure was maintained.

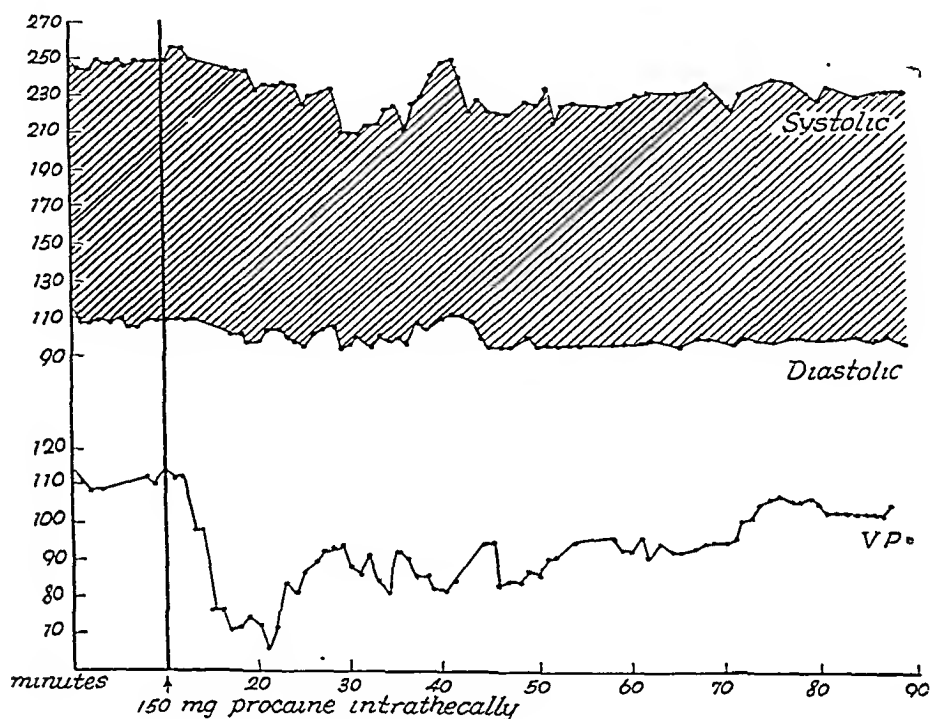


Fig. 13.—Graph of levels of blood pressure in patient F. F.

Figure 13 (F. F.) clearly shows that the venous pressure fell before the arterial pressure fell. On the other hand, the venous pressure rose significantly toward the control values, while the arterial pressure was continuing to fall to its lowest level. There was a small, and perhaps insignificant, drop in diastolic pressure in this patient.

#### SUMMARY

Simultaneous arterial and venous pressures were determined in 5 normotensive subjects. Twelve separate studies were made in 10 patients with a clinical diagnosis of essential hypertension. Control observations were made, and similar determinations were then made with high spinal anesthesia induced by 150 mg. of procaine hydrochloride. Observations were continued during recovery stages.

## CONCLUSIONS

In the majority of patients with essential hypertension, the arterial pressure fell before the venous pressure fell. In 1 case, the venous pressure fell without any significant decrease in arterial pressure. In only 2 cases, the venous pressure dropped first, and in these 2 cases the arterial pressures fell to their lowest levels before the venous pressures fell to their lowest levels. In these 2 cases, the arterial pressures were rising while the venous pressures continued to fall.

There is no constant time correlation between the falls of arterial and venous pressures during high spinal anesthesia in patients with hypertensive disease. The changes in arterial and venous pressures described are probably not causally related.

It is extremely unlikely that decreased venous return and diminished cardiac output are the causes of the fall in arterial pressure caused by high spinal anesthesia in either normotensive or hypertensive subjects.

The failure of these data to support the idea that decreased cardiac output is the cause of falls in arterial pressure gives additional support to the likelihood that these falls in arterial pressure are caused by interruption of vasomotor function.



## EXOPHTHALMOS AND THIOURACIL THERAPY

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THE GREAT majority of patients with thyrotoxicosis and exophthalmos appear to have recession of the exophthalmos after a satisfactory subtotal thyroidectomy. However, careful observation of the eyes of these patients with exophthalmometer measurements made before and after thyroidectomy<sup>1</sup> reveals that this appearance is misleading. Actually the protrusion of the eyeballs increases after thyroidectomy in 75<sup>1a</sup> to 97 per cent<sup>1b</sup> of the patients, but the disappearance of retraction of the lids and of associated eye signs gives the erroneous impression that the exophthalmos has been relieved.

It has been observed by Soley<sup>1a</sup> that progression of exophthalmos in patients with thyrotoxicosis was followed by intensification of the exophthalmos in 37 per cent fewer cases after roentgen therapy than after thyroidectomy. This decreased incidence was thought to be due to a slower return of the endocrine imbalance, present in thyrotoxicosis, to the normal balanced state. Since patients with thyrotoxicosis responded to thiouracil more slowly than to subtotal thyroidectomy,<sup>2</sup> it seemed worth while to analyze the results of exophthalmometer measurements on patients under treatment with thiouracil and propyl thiouracil.

Dobyns<sup>1b</sup> reviewed 11 cases in which patients with exophthalmic goiter were treated with thiouracil and followed carefully with exophthalmometric measurements. All patients experienced significant decrease in the basal metabolic rate and some increase in the prominence of the eyes ranging from 0.5 to 4.75 mm. Changes of less than 1 mm. were considered insignificant. However, 7 of the 11 showed progression of exophthalmos to the extent of 1.5 mm. or more.

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From the Department of Internal Medicine, University of Michigan.

1. (a) Soley, M. H.: Exophthalmos in Patients with Various Types of Goiter, *Arch. Int. Med.* **70**:206 (Aug.) 1942. (b) Dobyns, B. M.: The Influence of Thyroidectomy on the Prominence of the Eyes in the Guinea Pig and in Man, *Surg., Gynec. & Obst.* **80**:526, 1945. (c) Dobyns, B. M., and Haines, S. F.: Changes in the Prominence of the Eyes in Various Thyroid States, *J. Clin. Endocrinol.* **6**:633 (Oct.) 1946. (d) Rundle, F. F., and Wilson, C. W.: Development and Course of Exophthalmos and Ophthalmoplegia in Grave's Disease, with Special Reference to the Effect of Thyroidectomy, *Clin. Sc.* **5**:177, 1945.

2. Beierwaltes, W. H., and Sturgis, C. C.: Thiouracil and Propyl Thiouracil: A Comparative Clinical Study, *J. Lab. & Clin. Med.* **32**:392 (April) 1947.

## MATERIAL AND METHODS

One hundred and ninety-two exophthalmometer measurements were made for 28 successive patients with thyrotoxicosis under treatment with either thiouracil or propyl thiouracil. In addition one hundred and fourteen measurements were made for 12 patients with malignant exophthalmos. In 7 of the latter group the condition was toxic, and they were treated with thiourea derivatives alone, while the remaining 4, whose condition resembled the dissociated type of ophthalmopathy described by Hertz and Means,<sup>3</sup> were treated with both Lugol's solution and desiccated thyroid. One observer made over 75 per cent of all measurements. The readings were made usually at weekly intervals, on the same day each week, at 3 to 4 p. m. with a Hertel exophthalmometer. A single interocular distance was recorded for each patient, and care was used to have the eyes in the same vertical and horizontal positions at each recording. Each reading was made without reference to the previous reading.

## RESULTS

*Thyrotoxicosis Without Malignant Exophthalmos.*—Twenty-two of the 28 patients in this group were women, or 78 per cent. The age varied from 15 to 59 years, the average being 41 years. During the period of observation in which exophthalmometer readings were made, the basal metabolic rate fell an average of 20 per cent, with a corresponding change in the patient's clinical condition, including changes in the weight, pulse, pulse pressure and plasma cholesterol level. The period of observation averaged four months, with 21 patients followed for two or more months, 4 followed for nine or more months and 2 followed for seventeen months each. There was no significant change in the exophthalmometer readings during this time, the average change being an increase of 0.4 mm. for each eye. The minimum change considered significant is 1 mm.<sup>1a</sup> Three patients in this group had significant changes in the right eye, and 4 had them in the left eye. The changes in the right eye consisted of an increase of over 1 mm. in 1 patient and a decrease of over 2 mm. in 2 patients. In the left eye the changes were an increase of over 1 mm. in 2 patients and a decrease of over 1 mm. in 2.

*Malignant Exophthalmos.*—Criteria for the presence of "malignant exophthalmos" consisted of the presence of one or more of the following signs in patients with thyroid disease with exophthalmos: edema of lids, edema of conjunctiva with injection and corneal ulceration.

As would be expected,<sup>4</sup> males were in the majority, forming 64 per cent of the total. The average age was 33 years in this group of 11 patients. In 6 of the patients the condition was toxic, the basal metabolic

3. Hertz, S.; Means, J. H., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, *West. J. Surg.* **49**:493 (Sept.) 1941.

4. Mulvaney, J. H.: Exophthalmos of Hyperthyroidism: Differentiation in Mechanism, Pathology, Symptomatology, and Treatment of Two Varieties. *Am. J. Ophth.* **27**:589 (June); 693 (July); 820 (Aug.) 1944.

rates being over + 20 per cent and up to 85 per cent. In the other 5 patients it resembled more the dissociated type of ophthalmopathy,<sup>3</sup> with low metabolic rates.

In 7 patients the condition was considered toxic enough to require reduction of their basal metabolic rates with thiouracil or propyl thiouracil. For these patients exophthalmometer readings were made for an average of 5.7 months. Six of the 7 were followed for three months or more. In this group there was a significant average increase in the exophthalmos of 1.8 mm. in the right eye; in 5 it was 1.5 mm. or over. The average increase in the left eye was 1.7 mm., 3 showing a progression of 2.0 mm. or more. In only 3 was there subjective or objective improvement in orbital pain, edema or corneal ulceration.

Four patients with mild toxicity which permitted treatment with Lugol's solution alone were given desiccated thyroid in addition for relief of the exophthalmos. In these patients the average basal metabolic rate increased 13 per cent as compared with a decrease of 24 per cent in the preceding group. It should be emphasized that the group of patients with malignant exophthalmos who were treated with thiouracil or propyl thiouracil alone were much more toxic than the group who received Lugol's solution and desiccated thyroid. For the latter patients exophthalmometer readings were made for an average period of thirteen and a half months, 3 being followed for over eight months. In these patients a significant average decrease of 1.1 mm. for each eye was noted instead of an average increase of exophthalmos. Two of the 4 showed some objective or subjective relief of edema and other evidences of improvement.

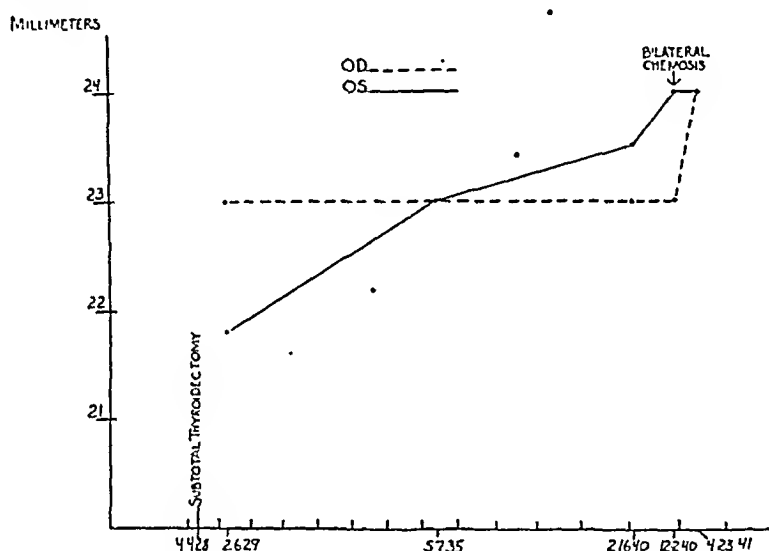
#### COMMENT

The results in 28 patients with thyrotoxicosis without malignant exophthalmos who were treated with thiourea derivatives differ from those which Dobyns<sup>1c</sup> found in a similar group of 11 patients. Seven of his 11 patients showed an increase of 1.5 mm. or more. He included a few patients, however, who apparently had malignant exophthalmos, 1 showing a progression of 4.75 mm. His observations in 233 patients after thyroidectomy<sup>1b</sup> indicated an increase in prominence of the eyes in all but 9, or 97 per cent. Two thirds of the patients showed a significant increase of over 1 mm. Soley<sup>1a</sup> found that 50 per cent of patients with exophthalmic goiter showed a significant increase in exophthalmos of 1.5 mm. or more in an average of ten months after thyroidectomy. Twenty-five per cent showed an increase of 0.5 to 1.0 mm. The results with thiouracil were better than either of these surgical results, an increase of over 1 mm. occurring in the right eye in 1 and in the left eye in 2 (a total of 10 per cent). These findings, as might be expected with a slower method of treatment of thyrotoxicosis, are

in accord with those reported by Soley<sup>1a</sup> after roentgen therapy. In his group only 20 per cent showed a significant increase.

It is possible that the separation of patients with "malignant" exophthalmos from those with nonmalignant exophthalmos in the evaluating of the statistics has resulted in some of the difference between the results reported here and those of Dobyns. I think, however, that this distinction is an important one since, as a rule, patients with malignant exophthalmos in whom the metabolic rates are high show an increase in exophthalmos regardless of the type of treatment used for the thyrotoxicosis.

An evaluation of the final position of the eyes in these patients will require many years of observation, as illustrated by the patient whose course is shown graphically in the accompanying chart.



Progressive exophthalmos in a patient followed for eleven years.

He experienced progressive exophthalmos for at least eleven years after a subtotal thyroidectomy had been performed. When he was last seen, typical malignant exophthalmos had developed.

#### SUMMARY

1. Twenty-eight patients with thyrotoxicosis and without malignant exophthalmos treated with thiourea derivatives alone had no significant average increase in exophthalmos when subjected to weekly exophthalmometer readings for an average period of four months.

2. Ten per cent of the patients showed a significant increase in exophthalmos, as compared with an incidence of 50 to 66 per cent reported by other authors after thyroidectomy and with an incidence of 20 per cent reported after roentgen therapy for thyrotoxicosis.

3. Seven patients with high basal metabolic rates and some evidence of malignant exophthalmos treated with thiourea derivatives alone

experienced a significant average increase in exophthalmos of 1.8 mm. over a period of observation of 5.7 months.

4. Four patients with low metabolic rates and malignant exophthalmos treated with Lugol's solution and desiccated thyroid showed no increase in exophthalmos over a period of 13.5 months.

5. It is important to distinguish between patients with malignant exophthalmos and those without it when evaluating changes in the eyes resulting from medical therapy for thyrotoxicosis.

# LOBAR ADENOCARCINOMA OF THE LUNG SIMULATING PNEUMONIA

Report of Two Cases

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RECENTLY, within a period of a few months, autopsy was performed in 2 cases at the Queens General Hospital, in both of which the true nature of an extensive pneumonic consolidation was not clearly recognized until microscopic study revealed diffuse adenocarcinoma. In neither of the cases could a primary adenocarcinoma be seen outside the lungs, nor could an exact origin from a bronchus be demonstrated. Though the condition is included in all anatomic classifications of pulmonary tumors, such cases are distinctly infrequent.

## REPORT OF CASES

CASE 1.—A 31 year old white housewife was admitted to the Queens General Hospital, complaining of shortness of breath and cough. Six months before admission, cough with scant expectoration developed. Two months later, the patient had pain in the right side of the chest, which was called pleurisy. One month after that, she visited the Department of Health Chest Clinic. A roentgenogram showed nodular fibrosis of the entire right side of the chest, with a thickened pleura, and increased pulmonic markings in the left lung (fig. 1). Reexamination one month later showed a similar picture on the right side and beginning nodular infiltration in the left pulmonary field. Examinations of concentrated sputum for acid-fast bacilli had negative results. In the two weeks before admission to the hospital, the cough and dyspnea grew severe. She was critically ill when admitted. The temperature was 101 F. The white blood cell count was 18,700, with 92 per cent polymorphonuclear leukocytes. A roentgenogram showed a diffuse dense homogeneous shadow throughout the entire right side of the thorax and a nodular type of parenchymal infiltration in the left lung (fig. 2). The previous roentgenograms of the chest were not available, and the clinical impression was that of tuberculous pneumonia of the right lung with spread to the left side. The patient died forty-eight hours after admission.

Autopsy revealed a completely solidified right lung, which, on macroscopic examination of sections, presented a dry grayish white surface with a pale yellow cast. This gross appearance suggested typical caseous tuberculous pneumonia. Throughout the left lung there was a nodular infiltration, the nodules being pale,

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Read before the New York Pathological Society, Feb. 28, 1946.

From the Department of Pathology, Queens General and Triboro Hospitals, Jamaica, Long Island, New York.

grayish white and 0.5 to 1 cm. in size (fig. 3). The pleural surfaces were studded with similar nodules. The mediastinal lymph nodes were not enlarged. The left adrenal gland was partly replaced by a firm white mass. The right kidney presented small white nodules, 0.5 to 1 cm. in size. Though the nodules in the kidney and the adrenal gland suggested metastatic tumor, no primary focus could be seen outside the lung in such sites as the thyroid gland, breast or ovaries. No one particular bronchus could be incriminated as a point of origin.

Microscopic examination of sections from the right lung revealed diffuse adenocarcinoma. The alveolar walls formed a supporting network for the tumor. The alveoli were lined by columnar tumor cells. These cells were, in many places,

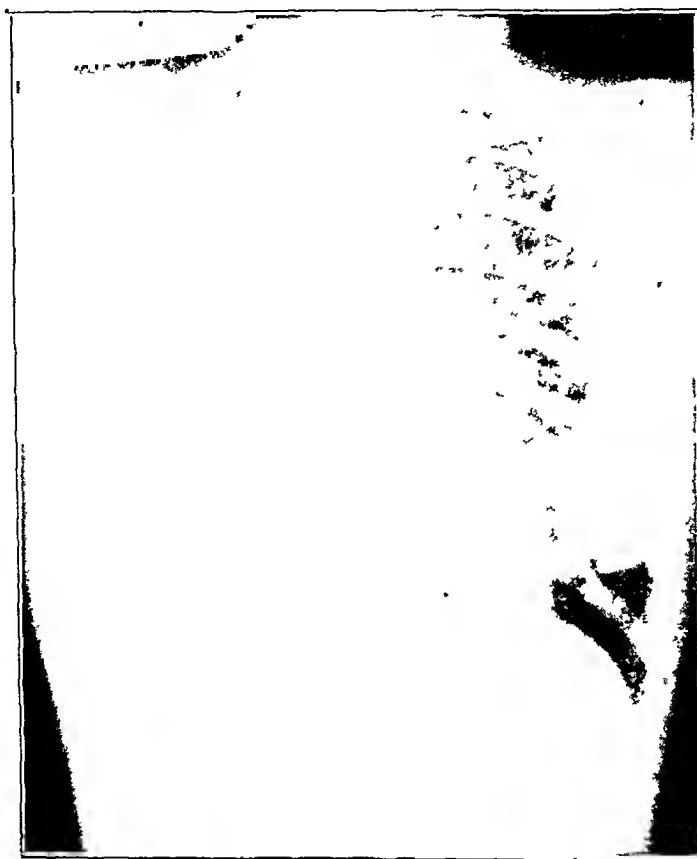


Fig. 1 (case 1).—Roentgenogram of the chest, three months after onset of cough. Nodular fibrosis of the right lung and increased pulmonic markings in the left pulmonary field are shown.

multilayered and grew in papilliferous folds projecting into the lumen. Within the alveoli lined by tumor cells, there were groups of free tumor cells, histiocytes, polymorphonuclear leukocytes and cellular debris. This alveolar content probably produced the yellow hue noted in the gross specimen on the cut surface. Not only the alveoli, but most of the bronchioles, were lined by tumor cells. The cells did not secrete mucus and were not ciliated. They exhibited considerable irregularity and presented many mitotic figures. There was no increase in elastic tissue in the alveolar walls. Tumor cells could be seen growing through the pulmonic alveolar vents. They were present in the peribronchial and perivascular lymphatic vessels and in the lymphatic vessels of the interlobular septums (figs. 4 and 5).



Fig. 2 (case 1).—Roentgenogram of the chest taken forty-eight hours before death, showing a diffuse homogeneous shadow throughout the right side of the thorax and a nodular infiltration in the left lung.

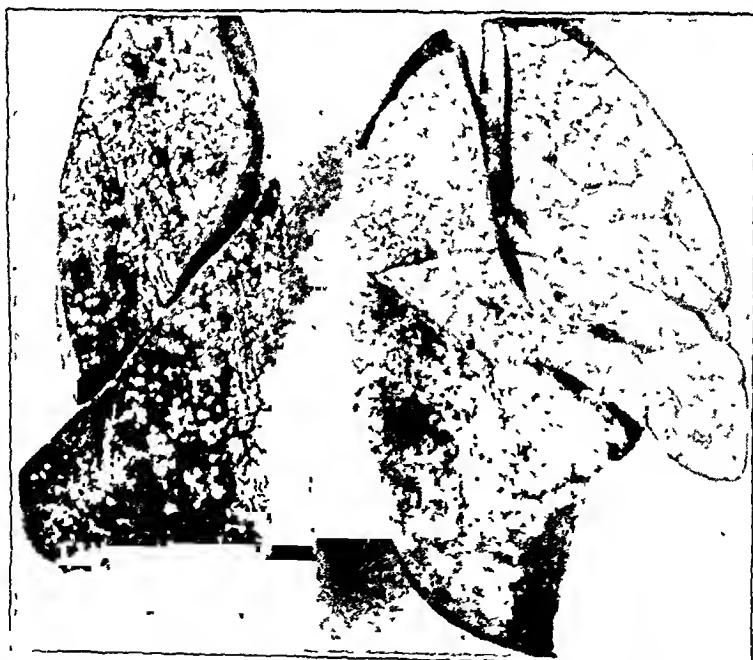


Fig. 3 (case 1).—Completely solidified right lung, with nodular infiltration throughout the left lung.



Sections through the left lung showed tumor cells within lymphatic vessels. The tumor nodules dispersed throughout the parenchyma were obviously metastatic. The presence of metastatic adenocarcinoma in the hilar lymph nodes, adrenal gland and kidney was verified in microscopic examination of the sections. An incidental observation was adenomyosis of the uterus.

The case was considered to be one of diffuse adenocarcinoma of the right lung, with metastases to the left lung, hilar lymph nodes, adrenal gland and kidney.



Fig. 4 (case 1).—Photomicrograph of tissue from the right lung, showing diffuse adenocarcinoma, with the tumor cells lining the alveolar walls.

CASE 2.—A 73 year old white woman was admitted to the Queens General Hospital, with a two months' history of cough and blood-tinged sputum. A roentgenogram, taken six days before admission, showed increased density over the lower half of the right lung; another area of increased density and radiating shadows in the upper lobe of the right lung and prominent bilateral hilar shadows. A diagnosis of tuberculosis was entertained. No positive reaction for tubercle bacilli was obtained in tests of the sputum throughout the subsequent five months' course. Thin straw-colored fluid accumulated in the right side of the chest, which

required repeated tapping. A roentgenogram, taken two weeks after admission, showed a nodular infiltration involving almost the entire right lung and radiating shadows in the upper lobe of the right lung, as previously noted, and prominent bilateral hilar shadows. There was, also, fluid at the base of the right lung, with a pneumothorax space inadvertently produced by a thoracic tap (fig. 6). Another roentgenogram, taken three weeks before death, showed clouding of the right pulmonary field, due to fluid, and accentuated pulmonary markings in the

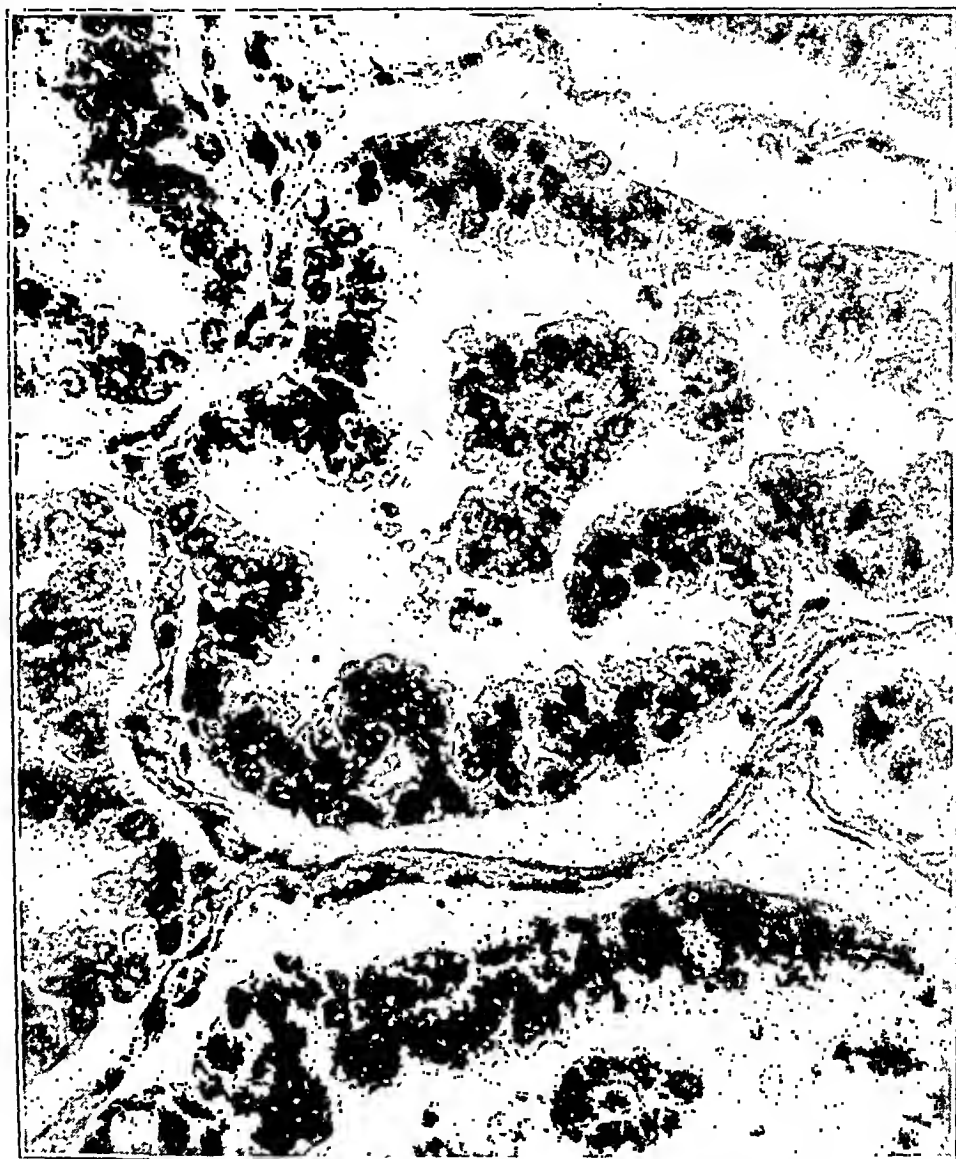


Fig. 5 (case 1).—Photomicrograph of tissue from the right lung. High power magnification of figure 4.

left side of the chest. A bronchoscopic examination was not made, because of the patient's poor condition. Death occurred five months after admission and seven months after the onset of symptoms. The diagnosis now favored was bronchiogenic carcinoma, though tuberculosis could not be excluded.

Autopsy revealed about 2 liters of sanguineous fluid in each pleural cavity. Macroscopic examination of sections revealed the right lung to be completely consolidated, the cut surface firm, gray and so mucoid that a gross diagnosis of lobar pneumonia caused by *Klebsiella pneumoniae* was made (fig. 7). Within

the lower lobe of the right lung, one old calcified tuberculous focus was recognized. The left lung was studded with small nodules of firm gray tissue. A lymph node in the right hilar region appeared infiltrated. There were small round nodules, averaging 0.5 cm., in both adrenal glands. As in the previous case, no primary focus could be seen outside the lungs, nor could any one particular bronchus in the lung be incriminated as a point of origin.

Microscopic examination of sections from the right lung revealed alveoli lined by mucus-secreting tumor cells. In addition to their mucus-secreting character, the tumor cells were tall, columnar, and nonciliated. They lined the alveoli in single layer, or the lining was multilayered. This lining was frequently thrown



Fig. 6 (case 2).—Roentgenogram of the chest taken about five months before death, showing nodular infiltration in the right lung and fluid at the base.

into papillary folds projecting into the acinar lumen, at times completely filling it (fig. 8). In many areas the tumor cells lost their columnar outline and were irregular and polyhedral, with large bizarre nuclei. Bronchioles retained their normal lining, though groups of tumor cells could be seen in the lumen. Fibrotic thickening of the alveolar walls was noted, as well as thickening of the interlobular septums and pleura. There was considerable deposition of anthracotic pigment. Tumor cells were seen in the lymphatic vessels.

In the left lung, tumor extension along peribronchial and perivascular lymphatic vessels was noted. Even in the lymphatic vessels, the tumor cells showed a tendency to line the lymphatic walls. Sections of lung also showed some traces of old tuberculosis. Microscopy confirmed the presence of metastatic mucogenic adenocarcinoma in the adrenal glands and revealed metastatic tumor in the liver.

The case was considered to be one of diffuse mucogenic adenocarcinoma of the right lung, with metastases to the left lung, hilar lymph nodes, adrenal glands and liver.

#### COMMENT

To clinicians, the cases presented herein offer a distinct problem in diagnosis. The disease is frequently thought to be some form of pneumonia. Careful consideration should include in the differential diagnosis the possibility of tumor infiltration in the lungs. To pathologists, the differentiation of these lesions from pneumonic consolidation offers considerable difficulty on gross inspection.

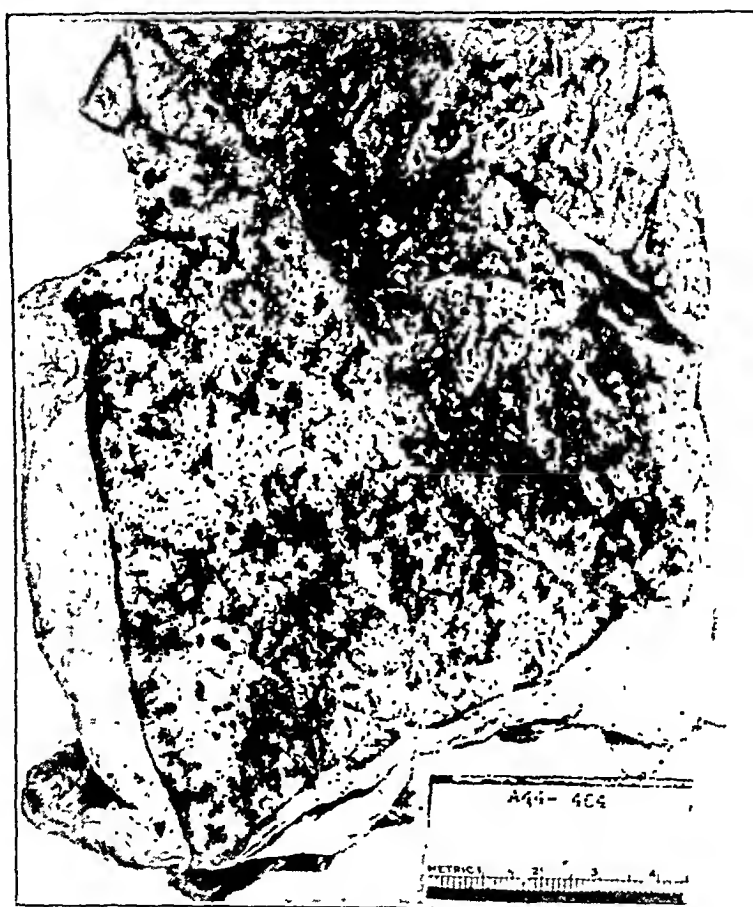


Fig. 7 (case 2).—Right lung, showing consolidation.

Such cases, also, present several points of interest:

1. Are they cases of primary adenocarcinoma of the lung or has a primary growth at some other site been overlooked?

A review of 4,500 consecutive autopsies at Queens General Hospital revealed 79 cases of metastatic adenocarcinoma to the lung, with the primary focus elsewhere in the body. Three of these cases presented what could be called massive consolidation of a lung by tumor. Two of the 3 were extremely interesting, because the only possible primary growth in each was a miniature carcinoma of the prostate gland. In the

third case the primary growth was in the breast. Histologically, the tumors grew at times diffusely and at times lining the alveolar walls.

Among the 4,500 cases, 26 instances of primary adenocarcinoma of the lung were noted, with the primary focus in a bronchus. None of these presented complete consolidation of a lung or lobe. Only the 2 cases described in this report presented lobar solidification, without a distinct point of origin.

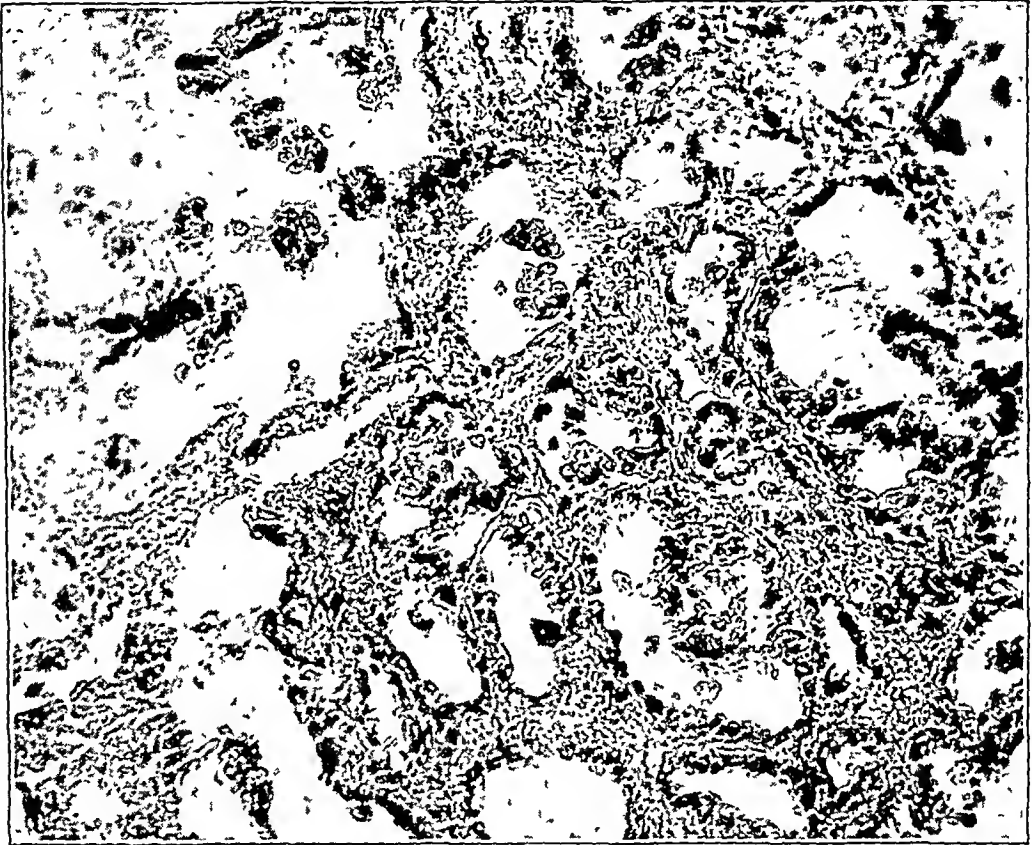


Fig. 8 (case 2).—Photomicrograph of tissue from the right lung, showing diffuse mucogenic adenocarcinoma, with the tumor cells lining the alveolar walls.

One could state simply that both metastatic adenocarcinoma and primary adenocarcinoma can, on rare occasion, consolidate a lung.

The growth pattern of the tumor, that of carcinoma cells lining the alveoli, does not help resolve the problem, since this is often seen in any adenocarcinoma in the lung, whether primary or metastatic.

Finally, reports of cases in the literature, reviewed by Neuberger and Geever,<sup>1</sup> support the contention that diffuse adenocarcinoma can occur in the lung without a demonstrable primary focus elsewhere.

1. Neuberger, K. T., and Geever, E. F.: Alveolar Cell Tumor of the Human Lung, *Arch. Path.* 33:551 (April) 1942.

2. If the primary site is in the lung, where is the point of origin of these tumors? Do they arise in the bronchial tree, or can they be called alveolar cell carcinomas?

Of the abundant literature on the subject, it will suffice for this presentation to point out: (a) The existence of an epithelial lining to the alveolar wall is still disputed, and, in general, negated by most authors. (b) A diagnosis of alveolar cell carcinoma can be made only if there is evidence of independence of the bronchial system.

Independence of the bronchial system cannot be established when there is extensive pulmonary involvement. Satisfactory proof can be obtained only from careful sectioning of a small tumor observed incidentally at autopsy or lobectomy. If evidence of independence of the bronchial system cannot be demonstrated, it follows that absolute proof of origin in the alveolar wall cannot be established.

3. May a theoretic origin for this tumor process exist in the well known instances of alveolar epithelization in human beings?

Bell,<sup>2</sup> and Geever, Neuberger and Davis<sup>3</sup> pointed out the many circumstances in which there occur thickening of alveolar walls, loss of function and lining of alveoli with a low cuboid cell. Whether this cell arises from the terminal bronchiole or the alveolar wall is still disputed.<sup>4</sup> The proliferation is a response to a chronic irritant. The type of proliferation may be said to be analogous to the polypoid growth of the intestinal mucosa during the healing of ulcerative colitis. The proliferating cell is clearly benign in appearance. No proof exists today to support the suggestion that these alveolar lining cells may be pre-cancerous.<sup>5</sup>

4. Could these tumors have multiple simultaneous points of origin?

The attempt to establish a multicentric origin for malignant tumors is always difficult. Metastases by way of lymphatic vessels, blood vessels and even direct implantation can occur rapidly and extensively. Certainly, in the 2 cases presented here, there is abundant evidence of lymphatic extension and, therefore, no justification for the assumption of a multicentric origin.

The possibility of simultaneous multiple points of origin from an alveolar lining, diffusely condemned by the action of some virus, bac-

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2. Bell, E. T.: Hyperplasia of Pulmonary Alveolar Epithelium in Disease, *Am. J. Path.* **19**:901, 1943.

3. Geever, E. F.; Neuberger, K. T., and Davis, C. L.: The Pulmonary Alveolar Lining Under Various Pathologic Conditions in Man and Animals, *Am. J. Path.* **19**:913, 1943.

4. Herbut, P. A.: Bronchiolar Origin of "Alveolar Cell Tumor" of the Lung, *Am. J. Path.* **20**:911, 1944.

5. Ikeda, K.: Alveolar Cell Carcinoma of the Lung, *Am. J. Clin. Path.* **15**:50, 1945.

terial agent or chemical, physical or other stimulant, raises the next question.

5. What, if any, is the relationship among diffuse or nodular adenocarcinoma of the lung, pulmonary adenomatosis in human beings, induced or spontaneous pulmonary tumors in mice and jagziekte infection in sheep?

Jagziekte in sheep,<sup>6</sup> probably a virus infection, presents a consolidated lung due to the lining of alveoli by a cuboid or columnar cell. At times this epithelium may proliferate in papilliferous fashion. The cells are benign in appearance and show no tendency to metastasize. However, there has been 1 case reported in the literature, by Aynaud,<sup>7</sup> in which metastases were said to have occurred.

Induced pulmonary tumors in mice have been shown to arise in multicentric fashion and to be independent of bronchioles (Grady and Stewart<sup>8</sup>). The nodules present groups of alveoli lined by cuboid or columnar cells. The cells usually have a benign appearance. Metastases seem to be infrequent. Wells, Slye and Holmes,<sup>9</sup> in discussing spontaneous tumors in mice, pointed out that they can, on rare occasion, metastasize. These authors stated that "it is extremely difficult to distinguish between benign and malignant tumors in mice, since some with a benign appearance may metastasize and others with a wilder growth, may remain localized."

Reports of cases of pulmonary adenomatosis in human beings have appeared in the literature<sup>10</sup> and have aroused considerable discussion in

6. Cowdry, E. V., and Marsh, H.: Comparative Pathology of South African Joogziekte and Montana Chronic Progressive Pneumonia of Sheep, *J. Exper. Med.* **45**:571, 1927. Dungal, N.: Epizootic Adenomatosis of Lungs of Sheep: Its Relation to Verminous Pneumonia and Joogsiekte, *Proc. Roy. Soc. Med.* **31**:497, 1938.

7. Aynaud, M.: Origine vermineuse du cancer pulmonaire de la brebis, *Compt. rend. Soc. de biol.* **95**:1540, 1926.

8. Grady, H. G., and Stewart, H. L.: Histogenesis of Induced Pulmonary Tumors in Strain A Mice, *Am. J. Path.* **16**:417, 1940.

9. Wells, H. G.; Slye, M., and Holmes, H. F.: The Occurrence and Pathology of Spontaneous Carcinoma of the Lung in Mice, *Cancer Research* **1**:259, 1941.

10. (a) Bell.<sup>2</sup> (b) Helly, K.: Ein seltener primärer Lungentumor, *Ztschr. f. Heilk.* **28**:105, 1907. (c) Oberndorfer, S.: Zellmutationen und multiple Geschwulstenstehungen in den Lungen, *Virchows Arch. f. path. Anat.* **275**:728, 1930. (d) Bonne, C.: Morphological Resemblance of Pulmonary Adenomatosis (Joogsiekte) in Sheep and Certain Cases of Cancer of the Lung in Man, *Am. J. Cancer* **35**:491, 1939. (e) Richardson, G. O.: Adenomatosis of the Human Lung, *J. Path. & Bact.* **51**:297, 1940. (f) Sims, J. L.: Multiple Bilateral Pulmonary Adenomatosis in Man, *Arch. Int. Med.* **71**:403 (Dec.) 1943. (g) Taft, E. B., and Nickerson, D. A.: Pulmonary Mucous Epithelial Hyperplasia (Pulmonary Adenomatosis): Report of Two Cases, *Am. J. Path.* **20**:395, 1944. (h) Wood, D., and Pierson, P.: Pulmonary Alveolar Adenomatosis in Man: Is This Same Disease as Joogsiekte in Sheep? *Am. Rev. Tuberc.* **51**:205, 1945.



recent years. The disease has been described as diffuse or nodular, but more frequently the latter. The cells lining the alveoli have been shown to be tall cuboid or columnar, at times growing in papilliferous fashion. Though the cells were considered benign in appearance, Wood and Pierson<sup>10h</sup> pointed out that in their case the cells showed active hyperplasia. Sims<sup>10f</sup> described his case as presenting, in areas, anaplasia, and Bonne<sup>10d</sup> stated that the lining cells in his case were dark and irregular, with mitoses. None of these cases presented metastases. Dacie and Hoyle<sup>11</sup> presented 1 case of the disease which they called malignant adenomatosis and which, they claimed, showed a fine gradation histologically from benign adenomatosis to definite invasive carcinoma. Another group of cases has been described in the recent literature, in which the authors pointed out a pattern of growth similar to pulmonary adenomatosis, but with more irregular cell structure and metastases.<sup>12</sup>

In all three groups of pulmonary adenomatosis, occurring in human beings, in mice and in sheep, the process seems to be benign epithelial hyperplasia, with possible malignant changes. An analogy may be drawn between these instances of pulmonary adenomatosis and multiple adenomatous polypi seen in the colon; they are benign though potentially malignant.

Though too little is known today to permit any clearcut conclusion, one can postulate that one or more nodules in pulmonary adenomatosis can be the precursor of a carcinoma. The observation of diffuse or nodular adenocarcinoma in the lung does not, of necessity, imply pre-existing adenomatosis.

#### SUMMARY AND CONCLUSIONS

Two cases of diffuse adenocarcinoma of the lung, with metastases, are presented.

The evidence would indicate the following conclusions:

1. The growths are primary in the lung, but metastases from a latent primary glandular focus outside the lung should be carefully excluded.
2. They arise from the mucosa of the bronchial tree beyond the larger bronchi, the point of origin being obscured by the extensive growth involvement.
3. A source of origin from preexisting epithelized alveoli cannot be proved.
4. A multicentric origin cannot be established.

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11. Dacie, J. V., and Hoyle, C.: Malignant Adenomatosis (Alveolar Cell Tumor) of the Lungs, *Brit. J. Tuberc.* **36**:158, 1942.

12. Herbut,<sup>4</sup> Ikeda,<sup>5</sup> Sweany, H. C.: A So-Called Alveolar Cell Cancer of the Lung, *Arch. Path.* **19**:203 (Feb.) 1935. Neuberger, K. T.: Primary Multiple Alveolar Cell Tumor of the Human Lung: Report of Case, *J. Thoracic Surg.* **10**:557, 1941.



5. To date, there is no proved relationship between diffuse adenocarcinoma of the lung and pulmonary adenomatosis.

Note—Since the manuscript was submitted, 2 additional cases have been encountered. In 1 a gross diagnosis of Friedländer's bacillus pneumonia was made at the time of the autopsy on the basis of the gross appearance. This seemed to be confirmed by the isolation of this organism on smear and culture. Subsequent histologic sections presented diffuse adenocarcinoma identical in every detail with the disease in the second case.

# Progress in Internal Medicine

## REVIEW OF NEUROPSYCHIATRY FOR 1947

STANLEY COBB, M.D.

BOSTON

THIS year marks the passing of Pierre Janet. He died at the age of 87, having courageously passed through war and through family bereavement in the last few years. In 1906 he was invited to come to America to give a series of lectures at the opening of the new buildings of the Harvard Medical School. These lectures became his famous book, "The Major Symptoms of Hysteria."<sup>1</sup> In 1936 he came back to Harvard's tercentenary and delivered a lecture, as full of sparkle and ideas as he was thirty years before. His work bridged the gap between centuries; with Freud and Meyer he brought psychologic medicine from its descriptive and classifying stage into its present dynamic state. His descriptions of psychic states were remarkable, but he was more interested in processes and in psychic developments. He did not believe in the arbitrary and artificial separation of neuroses from psychoses, considering it entirely false from the clinical standpoint. In his early years he was much interested in hypnosis. His last extensive work was a book on psychotherapy published in 1920. Few men have been as brilliant and enlightened on a subject for so many years.

A number of interesting books have appeared recently. Gordon Holmes,<sup>2</sup> the man who might be looked on as the dean of living neurologists, has written a little book giving his views on neurology and especially on methods of examination. "The Neurology of the Ocular Muscles" by David G. Cogan<sup>3</sup> is a two hundred page book of unusual merit. The author's wide clinical experience and skill in laboratory technic make the exposition of anatomy, physiology and symptomatology especially good. His concept of "tonus" as the "sum-total effect of the various neurochemical processes affecting the length of a muscle and, consequently, the position of an organ" is unusual but pleasing to the reviewer. It disposes of this vague term "tonus" by proclaiming

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1. Janet, P.: *The Major Symptoms of Hysteria: Fifteen Lectures Given in the Medical School of Harvard University*, New York, The Macmillan Company, 1907.

2. Holmes, G.: *Introduction to Clinical Neurology*, Baltimore, Williams & Wilkins Company, 1946.

3. Cogan, D. G.: *Neurology of the Ocular Muscles*, Springfield, Ill., Charles C Thomas, Publisher, 1948.

its identity with all muscular contraction. In fact Cogan goes on to say: "Movements of the eyes are brought about by increase in tone of one set of muscles or relaxation in tone of the antagonistic muscles, or as is usually the case by both." He discusses the labyrinthine control of the extraocular muscles, speaking of "maintained postural deviations" controlled by the otoliths and "postural movements" controlled by the semicircular canals. This is better terminology and is more physiologically understandable than "tone," especially because the author believes that the ocular muscles have no proprioceptive endings or nerves. Knowledge of the position of the eyeballs depends on vision. The facts arrayed to back up this opinion are convincing. The text is arranged according to physiology and signs. Disease entities are not emphasized. The book is well illustrated by sixty-nine diagrams and photographs.

Another notable book is "Brain and Intelligence" by W. C. Halstead,<sup>4</sup> of the University of Chicago. His aim is "to set up an operationally defined conception of biological intelligence in terms of number and kind of factors involved." Thirty control subjects and 207 persons with injured brains were examined by means of a battery of tests. The results were correlated, and the intercorrelations were treated by factor analysis. This yielded four factors interpreted as "C," a central integrative field factor, "A," a basic ability for abstraction, "P," an undistorted "power" factor of the functioning brain closely related to affect and "D," a directional factor for the exteriorization of intelligence. These gave a quantitative basis for estimating intelligence which the author then applied to patients. He worked out an "index of impairment" for patients who had undergone lobectomies, lobotomies and head injury. He concludes that the frontal lobes are "the areas most essential to biological intelligence." No short review can do more than indicate that here is an important piece of work pointing the way to new and better methodology in a field too much influenced by unreliable clinical impressions.

Leon Saul<sup>5</sup> in his "Emotional Maturity" has undertaken one of the most difficult of tasks. He has endeavored to present a description of the mind as a rough equivalent of the gross anatomy and physiology of the body. His training in neurophysiology, psychiatry and psychoanalysis has fitted him well for the task. He respects the scientific method and defines terms. "Mind" is to him "the activity of the highest level of the brain, which we perceive and experience as our thoughts

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4. Halstead, W. C.: *Brain and Intelligence: A Quantitative Study of the Frontal Lobes*, Chicago, University of Chicago Press, 1947.

5. Saul, L. J.: *Emotional Maturity: The Development and Dynamics of Personality*, Philadelphia, J. B. Lippincott Company, 1947.

and feelings and express in psychologic terms." Man is an organism, reacting and striving. The psychodynamic study of this biologic activity is the field of the psychiatrist who would understand personality. Psychodynamics is the study of how the mind works or a study of the forces which motivate us.

It has long been the custom among psychiatrists to explain abnormal behavior on the vague basis of "emotional immaturity." Saul pins this down in his first chapter, saying:

We have now mentioned eight of the major aspects of the emotional development of man and some of the characteristics of maturity to which each leads. This list is not exhaustive; these aspects are interrelated and are not all on the same level. But we have tried to discern some of the forces in the personality which are basic and from which the many other attributes of maturity are derived. We have seen that when the development is fulfilled the adult is *predominantly* independent and responsible, with little need to regress, and also is giving and productive, although still able to relax and to receive normally; he is cooperative rather than egotistical and competitive; he is in relative harmony with his conscience, which easily integrates with his mature feelings and behavior; his sexuality is free and integrated with mating and responsible productive activity, both sexual and social; his hostility towards others and toward himself is minimal but is freely available for defense and constructive use; his grasp of reality is clear and unimpaired by the emotional astigmatism of childhood; and freed from childhood patterns, he is discriminating and highly adaptable. And among the many results of such development, his anxiety is at a minimum.

These cardinal points are taken up extensively in eight separate chapters.

"Man's suffering on this earth is caused predominately by man himself and is a manifestation of his emotional immaturity." This epigrammatic sentence from page 12 seems to express the main theme of the book. It is not far from being the key to the neuroses which is expressed on page 316 as "the tendency in everyone to regress under stress to earlier childhood ways of thinking and reacting." Neurosis is defined as "a failure of adaptation and a disturbance of the patient's emotional development." The essence of neurosis is said to be (page 291) "the undue predominance of untoward childhood reactions." Saul wisely emphasizes that although he is writing about the psychic determinants of neurosis there are others of great importance, such as heredity, physical constitution and fetal development.

The book is readable, forceful and informative. While it attempts a synthesis that is impossible in 1948, it makes a step forward in clarifying the concept of the neuroses. There is a lighter touch in certain phrases and illustrations that is welcome. Some of the diagrams are helpful, while others are rather overwhelming. The "first approximation" of expressing neurosis in a mathematical formula shows that the author has reached maturity and does not fear criticism!

## SEXUAL BEHAVIOR

Kinsey, Pomeroy and Martin,<sup>6</sup> three nonmedical scientists from the University of Indiana, have given to medicine and especially to psychiatry some much needed facts. When a physician was asked about sexual habits, normal and abnormal, he usually had little to fall back on except somewhat impressionistic clinical experience. Medical literature did not give the answers he needed. Now this book on "sexual behavior in the human male" supplies the data needed. It is based on interviews with 5,300 white men, representing six hundred and ninety-eight samples of different population. The senior author is a professor of zoology, and the approach is taxonomic, implying that the author's interest is merely to name, describe and classify. Mostly they stick to their last and do a remarkably good job. Occasionally they make challenging statements. For example, in discussing the so-called perversions, they say: "It may well be questioned how far an individual is responsible for his behavior when he conforms to the pattern of his social level, even though he may thereby be involved in a transgression of the law" (page 681).

Some of the clinical problems that face the physician are described (on page 578) as follows:

A list of the social problems which most often arise out of human sexual activity would give first places to venereal disease, bastardy, rape, and the contribution by adults to the delinquency of minor children. On the other hand personal conflicts most often develop over masturbation, oral contacts and the homosexual. These are the three that need especial help—not because they are rare, but because they are widespread, and because nearly every male in the population is at one time or another involved in one or more of them. These are the three that are most often encountered by the clinician, not because men are frequently abnormal or recently become perverse, but because all three of these are part of the basic biologic pattern of mammalian sexual behavior, and because no legislation or social taboos have been able to eliminate them from the history of the human animal.

The point for the physician to remember is that oral-genital stimulation is not rare and is not "unnatural." It occurs in most mammals, and it occurs, according to Kinsey, in 60 per cent of the case histories of the more educated people, in 20 per cent of those persons of the high school level of education and in 11 per cent of those of the poorly educated. These last are the ones who have most taboos and look on the sex habits of the educated as "perverse" and "unnatural." They also taboo nakedness in intercourse, which can hardly be called "unnatural." Doubtless because of the strong taboo, there is much concealment in their histories on this point, and the

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6. Kinsey, A. C.; Pomeroy, W. B., and Martin, C. E.: *Sexual Behaviour in the Human Male*, Philadelphia, W. B. Saunders Company, 1948.

figures should be raised. The subject is important because many divorces are caused by this "perverted" sexual behavior. Considering the behavior medically, it would seem more scientific not to say that the act in itself is abnormal or unnatural but to lay stress on the individual situation and on the selfishness or "cruelty" of the spouse who insists on such acts in spite of the disturbing effect on his partner.

The book has been so widely reviewed in the general press that I will not transcribe much of the material. It is given abundantly in tables and should be read in the context and with an understanding of the statistical procedures to be of full value. A few of the more important data may be summarized as follows:

The frequency of sexual outlet is indicated by the data on the number of orgasms per week of single white males. The average is highest for those between the ages of 15 and 20, a little over three times a week, and drops off gradually to 1.9 for those between 41 and 45. In the poorly educated group the average runs about a fifth higher than in the well educated group throughout the different ages. This may mean that conscientious scruples are more effective in the educated group or that satisfactions on a more intellectual plane take up some libido by sublimation. It might be explained in other ways. Kinsey has some data to show that devoutly religious males have much less extramarital intercourse (table 129).

In the poorly educated group between the ages of 15 and 35 masturbation averages about once a week and intercourse about twice a week. In the group with some college education this is reversed, intercourse averaging less than once a week and masturbation about twice. The highest rate of masturbation is found among those 15 years old in the educated group, the average for the number of times being 2.7 per week. The highest average rate of intercourse is found among the low education group aged 21 to 25, with an average of 2.3 per week.

The method of interviewing is given in chapter II. This is an admirable exposition of what an interview should be when the object is fact finding in connection with a frequently embarrassing subject. The success of these men seems to have been due to their extraordinary patience, great decency and human understanding. They seem to have been able to lead another man "into exposing his activities and his innermost thoughts." "Failing to win that much from the subject," it is stated, "no statistical accumulation, however large, can adequately portray what the human animal is doing." In other words, unless the interviewing is successful and brings out a good approximation of the truth, the whole project is useless. One is convinced that the authors have done a good job and that most of the data are valid and important.

A definition of "truth" in this situation is another matter. The authors are self-avowedly taxonomists and not psychiatrists or psycho-

analysts. Professional psychiatrists with training in psychoanalysis might bring up the question as to whether the reports of many of these persons actually were true, because in the sexual sphere repression may cause some very thorough forgetting and even false memories. Just this point is brought up emphatically by Kubie<sup>7</sup> in his trenchant review. The question cannot be answered until sample cases have been studied by psychiatric technic with a view to bringing out the repressed and subconscious material. To what degree such a study would modify the conclusions of the present book remains a matter of speculation. One might guess, however, that the main facts about overt sexual activity as here stated would stand up well, whereas the data concerning subjective responses, fantasies, childhood memories and homosexual activities might be modified considerably.

It is of importance to psychiatry to learn that in this taxonomic study the main postulates of psychoanalysis concerning infantile sexuality have been verified. Sexuality before the age of 8 seems to be diffuse and polymorphous. All sorts of varied stimuli set up sexual reactions. Orgasm in the male (except for ejaculation) has been observed at 5 months and frequently at 2 years. One 4 year old had twenty-six orgasms in twenty-four hours. As adolescence comes on, at 8 or 10 years, the stimuli causing erotic response become more concentrated in the genital organs. The concept of a "latency period" is not substantiated by Kinsey's observations.

There is no evidence that marked sexual activity in younger persons tends to make for less potency later. In fact, the evidence points to the opposite. The lower the cultural level the more premarital and extramarital intercourse is found. The lower group considers the upper "perverted" and the upper considers the lower "immoral"! About 85 per cent of all males have premarital intercourse. Between 30 and 45 per cent have extramarital relations. Some sort of homosexual experience is reported by 37 per cent of the total group. The incidence is 70 per cent in the lower education group at 16 years of age and 30 per cent in the higher education group. A great many of the homosexual contacts are incidental; the homosexual response is most often definite and repeated in preadolescence (6 to 10), through the "teens" and up to 25 years of age. Over 20 per cent of males between the ages of 6 and 26 are more than incidentally homosexual (fig. 170).

This brings up the question of what is "normal." If all homosexual activity is to be called abnormal, what can be done about it? Kinsey puts it this way:

It means that at least 13% of the male population would have to be institutionalized and isolated, if all persons who were predominately homosexual

7. Kubie, L. K.: *Sexual Behavior in the Human Male*, by A. C. Kinsey; W. B. Pomeroy and C. E. Martin, book review, *Psychosom. Med.*, to be published.

were to be handled in that way. Since about 34% of the total population of the United States are adult males, this means that there are about six and a third million males in the country who need such isolation.

The statistical concept of "normal" in this case certainly is a challenge for physicians, penologists and sociologists. Not enough differentiation is made between the sexually active youth who is giving everything a rather thoughtless try and the older, compulsive homosexual. To the psychiatrist the numerical data suggest that what one is interested in particularly should be the individual case. By studying in each case what the endocrine and psychologic factors may be, the physician might decide who is "sick" and to what degree. Likewise the penologist can decide who is "good" and who is "bad." Both want to know how dangerous a given man is to the accepted habits of the community. Careful consideration should be given to what is meant by "normal," "good" or "well," as opposed to "abnormal," "bad" or "sick."

#### CAUSES OF MENTAL DEFICIENCY

The older books on amentia lay emphasis on only two causes, inheritance and syphilis. For this reason the prevention and treatment of feeble-mindedness have often been taken up with a pessimistic attitude by physicians. Educators have been more hopeful and have methodically gone ahead with what could be done for the individual ament. Gesell<sup>8</sup> broadens the concept a great deal, classifying developmental aberrations as (1) defective development, due to (a) aplasia, malformation and degenerative diseases or (b) lesions following trauma, infection, toxic agents, anoxia and irradiation, and (2) deviated development due to prematurity, endocrine disorder, sensory and motor handicaps, abnormal experience and personality defects.

The last two items bring in the great field of psychogenesis, which is discussed later under child psychiatry. The other categories have been made clearer by several recent investigations. In the endocrine field there is evidence that cretinism is associated with maternal hypothyroidism and that mongolism is related to maternal pituitary disorder.<sup>9</sup> More strictly in the field of genetics, Professor Muller, of the University of Indiana, has been recently awarded the Nobel Prize for showing that radiation may cause changes in the genes. This makes one think of various sorts of radiation as possible factors in causing mal-

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8. Gesell, A. L., and Amatruda, C. S.: *Developmental Diagnosis*, ed. 2, New York, Paul B. Hoeber, Inc., 1947.

9. Benda, C. E.: *Mongolism and Cretinism: A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency*, New York, Grune & Stratton, Inc., 1946.



development of the nervous system. Incompatibilities in blood groups with respect to the Rh factor have been shown to be responsible for damage to the nervous system of newborn babies. The presence or absence of the Rh factor is apparently transmitted through the genes.<sup>10</sup>

Encephalitis of various sorts has been proved to be a cause of mental deficiency. Toxoplasmosis is one of the most recently recognized. Children having hydrocephalus, intracerebral calcification and chorioretinitis should be suspected, and they should be tested by serologic methods and by means of animal inoculation.<sup>11</sup> Rivers<sup>12</sup> lists fifteen viruses that may cause human encephalitis. Many of these affect children and may cause the various behavior disorders and mental defects with which pediatricians are familiar. Some of these diseases may be borne by mosquitoes<sup>13</sup>; both the equine encephalomyelitis and the "St. Louis type" of encephalitis have been isolated from *Culex tarsalis*. Equine encephalitis is commonest in children under 5 years of age. "Japanese B" encephalitis occurs in cows, horses, goats and fowl, and epidemiologic data suggest that the virus is carried by mosquitoes.<sup>14</sup> Although nothing is known of the organism responsible for Economo's disease, which used to be the common form of encephalitis, much new knowledge is coming to the clinician about other forms of encephalitis. A certain number of cases of mental defect are thus being explained.

Diseases of the mother causing injury to the fetus have been long known, but that rubella was one of these was brought to light only six years ago in Australia.<sup>15</sup> Gregg has shown that a long list of "congenital" defects can be laid to this cause, including deafness, microcephaly and mental retardation. A growing literature shows that this is an important source of amentia. Ingalls and Davies<sup>16</sup> believe that other

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10. Levine, P.; Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy: Its Possible Bearing on Etiology of Erythroblastosis Foetalis, *J. A. M. A.* **116**:825 (March 1) 1941.

11. Kabler, P., and Cooney, M.: Toxoplasmosis, *Minnesota Med.* **30**:637, 1947. Toxoplasmosis, editorial, *New England J. Med.* **237**:346, 1947.

12. Rivers, T. M.: Virus Diseases of the Nervous System, *J. A. M. A.* **132**:427 (Oct. 26) 1946.

13. Meyer, K. F., and Eddie, B.: Knowledge of Human Virus Infections of Animal Origin, *J. A. M. A.* **133**:822 (March 22) 1947.

14. Sabin, A. B.: Epidemic Encephalitis in Military Personnel: Isolation of Japanese V Virus on Okinawa in 1945; Serologic Diagnosis, Clinical Manifestations, Epidemiologic Aspects and Use of Mouse Brain Vaccine, *J. A. M. A.* **133**:281 (Feb. 1) 1947.

15. Wesselhoeft, C.: Rubella, *New England J. Med.* **236**:978, 1947.

16. Ingalls, T. H., and Davies, J. A. V.: Mongolism Following Intercurrent Infectious Disease in Pregnancy, *New England J. Med.* **236**:437, 1947.

infections of pregnant women, such as influenza and mumps, may cause mongolism in the child if the infection occurs during the second month.

#### CHILD PSYCHIATRY

The groundwork for child psychiatry was laid forty years ago by Binet, Freud, Eichorn and Healy. The important influence of Adolf Meyer is emphasized by Helen Witmer<sup>17</sup> in her introduction to "Psychiatric Interviews with Children"; she says that he was interested in the problem in the 1890's and gave child psychiatry a start in the early part of this century by his dynamic psychology. Healy directed the first child guidance unit, the Juvenile Psychopathic Institute in Chicago, which opened in 1909. His career since then until his recent retirement has been one of leadership in a rapidly expanding field. Describing the recent changes in attitude and practice, Witmer says (page 12):

By the end of the mid-nineteen-thirties, however, a change in child guidance psychiatry was in process. The stimulating conceptions derived from psychoanalytic work with young children were beginning to influence practice. Play was found to be an adequate substitute for discussion as a means of revealing young children's difficulties and giving help in overcoming them. Psychiatric interviews themselves became less intellectual, as the implications of the dynamic theory, for therapy as well as for etiology, became apparent. Less emphasis was put on symptoms, as expressed in behavior and personality traits, and more on feelings and desires. In short, psychiatric study and prescription gave way to psychiatric treatment.

The therapists took off their good clothes and their adult veneer and got down on the nursery floor with the children to see what they were up to. By doing this they learned the language of the child, verbal and nonverbal, and made a relationship which they used not only for diagnosis but for therapeutic ends. The extraordinary patience of the therapists as well as their feeling for the child and their insight into his disordered personal relations frequently bring about remarkable improvement in behavior. The case histories recounted in Witmer's book and in the first two volumes of "The Psychoanalytic Study of the Child"<sup>18</sup> give good evidence of this.

The technic of child analysis is different from that of adult psychoanalysis. The child cannot be expected to talk about his problems. Mahler<sup>19</sup> says:

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17. Witmer, H. L.: *Psychiatric Interviews with Children*, New York, The Commonwealth Fund, 1946.

18. Freud, A.; Hartmann, H., and Kris, E.: *The Psychoanalytic Study of the Child: An Annual*, New York, International Universities Press, Inc., 1945, vol. 1; 1946, vol. 2.

19. Mahler, M. S.: *Child Analysis*, in Lewis, N. D. C., and Pacella, B. L.: *Modern Trends in Child Psychiatry*, New York, International Universities Press, 1945.

We have plenty of valuable substitutes for it in the use, as analytic material, of all productions and functions of the child: play, drawing, dramatic acting, competitive games, gymnastic stunts, handy craft, story telling, continual day dreams, fantasies, and the like, are all our tools. We leave the initiative entirely to the child and, though we participate, we try to get the lead from the patient in order that we may avoid introducing elements into the situation not pertinent to the child.

The application of psychoanalysis to childhood problems had beginnings as far back as 1909, when Freud analyzed the phobia of a 5 year old boy. Psychoanalysts from the beginning dealt with childhood memories in their adult patients, and these memories pointed to the great importance of early childhood in the development of future patterns of behavior. No direct attack on the problem was made until Anna Freud, a schoolteacher, took psychoanalysis into the educational field. She published "An Introduction to the Technique of Child Analysis" in 1928,<sup>20</sup> and in 1932 started the "*Zeitschrift für Psychoanalytische Paedagogik*." These beginnings were interrupted in 1938 by the Nazis. Freud and his daughter moved to London, where he died in 1939. She went on with her work among children and made a great contribution both to the war and to psychology by studying the displaced children and describing their reactions to separation from parents, foster care, bombing and other stresses. These observations of comparatively normal children under environmental difficulties have given Anna Freud material for important contributions.<sup>21</sup> The point that strikes the reader most emphatically is that separation from father and mother, especially the mother, is more devastating to the child than bombing. The author emphasizes the great importance of the first five years of life in the development of personality. "In the beginning of life the child is ruled merely by its own desires. It next learns to renounce gratifications for the sake of the parents . . . . In the next phase it begins to share the parents' valuations." When it has learned to act on these new attitudes which were taken on because of love for the parent, "the child has established within itself a moral center—a conscience or superego." This transformation from primitive instinctive behavior to moral code seems to take place without effort or special knowledge in a secure, affectionate family setting. In residential nurseries or in other infant asylums, no matter how well run,

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20. Freud, A.: *An Introduction to the Technique of Child Analysis*, Nervous and Mental Disease Monograph Series 48, New York, Nervous and Mental Disease Publishing Company, 1928.

21. Freud, A., and Burlingham, D.: *Infants Without Families: The Case For and Against Residential Nurseries*, New York, International Universities Press, 1944. Freud, A.: *The Ego and the Mechanisms of Defense*, translated by C. Baines, *ibid.*, 1946.

this parental relationship is lacking, and the lack leads to pronounced disturbances.

René Spitz<sup>22</sup> has described a depressive syndrome that occurs in infants separated from their mothers. He cites cases in which children separated at 7 to 11 months of age soon became apprehensive, sleepless, weepy and withdrawn. They showed little interest in their environment and lost appetite and weight. Later retardation in development became obvious and the general picture of dejection might go on to stupor. If the mothers can be brought back within three months, the process is quickly reversed, with a return to normal. When the mother was away much longer, most of the children showed considerable retardation in bodily development, motor ability and speech. At 2 years of age only 5 out of 21 could walk. Some showed a picture of "stuporous catatonia"; 31 out of 91 children in one foundling home died in spite of apparently adequate hygiene and general care.

The mention of catatonia brings up the moot question of childhood schizophrenia. This has been long and carefully discussed, the most recent contribution being by Despert,<sup>23</sup> who gives a good summary and references. Children who present bizarre behavior, resembling what in an adult would certainly be diagnosed as schizophrenic, fortunately are rather rare. Large clinical centers, however, have collected impressive series of cases. The unanswered question is whether these children suffer from encephalopathy, from a congenital disorder, as some who use the term schizophrenia imply, or from a severe social maladjustment. The theory that they suffer from the last, at least in some cases, receives support from the work at the James J. Putnam Children's Center in Boston, directed by Beata Rank and Marian Putnam.<sup>24</sup> Here a meeting was held in November 1946 of the Child Psychiatry Committee of the American Society for Research in Psychosomatic Problems. At this meeting it was demonstrated that some children who showed grossly regressive behavior and seemed largely out of contact could be improved by intensive and prolonged psychotherapy in which the development of a warm relationship with the therapist and the use of play technics were the principle elements. Loss of the mother before the age of 2½ years seems to be an important cause or at least a precipitant of these regressive syndromes. Much more work is needed to improve diagnosis so that appropriate cases may be chosen for therapy. Long range follow-up

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22. Spitz, R. A.: *Anaclitic Depression*, in Freud, A.; Hartmann, H., and Kris, E.: *Psychoanalytic Study of the Child*, New York, International Universities Press, Inc., 1946, vol. 2, p. 313.

23. Despert, J. L.: *The Early Recognition of Childhood Schizophrenia*, *M. Clin. North America* **31**:680, 1947.

24. Putnam, M. C.: *Case Study of an Atypical Two-and-a-Half-Year-Old*, *Am. J. Orthopsychiat.* **18**:1-30 (Jan.) 1948.

will be needed to see whether or not these children become schizophrenic later in life. But it looks as if at least some children could be benefited by psychologic means. Besides saving some children from a long life in hospitals for the mentally ill, this work might throw some light on the cause of schizophrenia. The work of Kempf,<sup>25</sup> Sullivan<sup>26</sup> and Rosen<sup>27</sup> indicates that some adult schizophrenics can be greatly improved by careful intensive and prolonged therapy. By this is meant getting down to the level of the patient and understanding his regressive ways and talk. A relationship with him is set up, and he is given support, so that he has a backing to throw off his great fear and inordinate sensitiveness. The treatment is strongly reminiscent of what has to be done for children with bizarre and regressive behavior.

A discussion of the even earlier relationship of mother and infant was organized by the Josiah Macy, Jr. Foundation on March 3 and 4, 1947, in New York.<sup>28</sup> Pediatric psychiatrists, psychologists and anthropologists met to talk about various aspects of the earliest relationships of parents and their offspring, especially the plan of having the infant continuously with its mother from the time of its birth. This is the "rooming-in" controversy that has been going on in obstetric hospitals. In the past twenty-five years the number of babies delivered in hospitals has increased enormously. It is the fashion to go to a hospital to have the baby delivered. Thus delivery, which is normally a physiologic event, has become a surgical procedure, with all that that implies in meticulous cleanliness and in restricted personal contacts. The baby is isolated and put on a strict regimen. "Rooming-in" is the reaction against all this. The child is left in the mother's room. She takes over its care as rapidly as she can and is instructed by the nurse in the necessary steps. The consensus was that from the psychologic standpoint rooming-in was advantageous. The anxiety of the mother was reduced, the baby was better cared for by being individualized, the transition from hospital to home was easier, the physician could observe the mother-child relationship better and the "rejecting" attitudes which may be developed in an orthodox obstetric regimen were avoided. The attitude of "training" is supplanted by one of permissive and affectionate care. Some interesting ethnologic observations on other races were brought in to support the thesis. One wonders how much memory the

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25. Kempt, E. J.: *Psychoanalytic Treatment of Dementia Praecox*, *Psychoanalyt. Rev.* **6**:15-58, 1919.

26. Sullivan, H. S.: *Conception of Modern Psychiatry*, *Psychiatry* **3**:1-117 (Feb.) 1940 [pp. 69-82].

27. Rosen, J. N.: *A Method of Resolving Acute Catatonic Excitement*, *Psychiatric Quart.* **20**:183, 1946.

28. Senn, M. J. E.: *Problems of Early Infancy*, New York, Josiah Macy, Jr. Foundation, 1947.

infant can have of the events of the first ten days! It seems reasonable to suppose, however, that the sort of relationship started in these days between mother and child may be important in the future development of the child, especially in avoiding sensitiveness to fear and other harmful habit formations. Chisholm<sup>29</sup> goes so far as to say: "It is possible to bring up children who will in fact be able to live pleasantly and comfortably with other people without having to fight each other almost continuously as we and all our ancestors have always done." Saul<sup>5</sup> has a similar idea when he says: "No preventive step is more important than formulating our knowledge of aggression in the interests of diminishing this central threat to mankind."

#### THE PYRAMIDAL TRACT AGAIN

Although the pyramidal tract and the cortical motor area was discussed at length in this review for 1945,<sup>30</sup> papers have since appeared which increase the understanding of the mechanism. Bosma and Gellhorn<sup>31</sup> showed in a series of experiments on monkeys that stimulation of a cortical focus results in definite patterns of movements if condensor discharges lasting ten seconds are used. This is long enough to permit facilitation, and it gives a more physiologic picture of what normally takes place. The popular method of brief threshold stimulation led to the erroneous theory that the cortex was made up of a mosaic of discrete points, each representing a definite unit of musculature. The principle of reciprocal innervation, with either inhibition of antagonists or cocontraction, was proved. The theories of Huxley, Jackson and the observations of Sherrington are thus substantiated for cortical function.

Walshe is at his polemic best in two papers in *Brain*. The first is "On the Notion of the 'Discrete Movement.'"<sup>32</sup> Here he points out that a discrete or isolated muscular movement is a physiologic impossibility. Voluntary movement is an enormously complex affair. The thesis that the pyramidal tracts innervate "discrete" or "isolated" movements and that the extrapyramidal tracts innervate complex postural movements is not tenable. The movements arising from the pyramidal system may differ in degree from those of the extrapyramidal system, but it is a quantitative and not a qualitative difference. The misunderstanding

29. Chisholm, B.: Revolutionary Changes in Sources of Security, *Christian Register*, August 1947, vol. 126.

30. Cobb, S.: Review of Neuropsychiatry for 1945, *Arch. Int. Med.* **77**:576 (May) 1946.

31. Bosma, J. F., and Gellhorn, E.: Organization of the Motor Cortex of the Monkey Based on Electroencephalographic Studies, *Brain* **70**:127, 1947.

32. Walshe, F. M. R.: On the Notion of the "Discrete Movement": A Critical Note, *Brain* **70**:93, 1947.

arises largely from the interpretation of experiments on stimulation, in which the motor and premotor areas of monkeys and other mammals were stimulated with new and refined technics. From the motor area brief twitches of part of a muscle have been recorded (never a single twitch similar to the reaction of a stimulated ventral horn cell). These short and localized responses have been interpreted as physiologic. There is reason to believe that they are not in any way similar to the normal contractions set up by the motor cortex. The electrical stimulus used in the laboratory experiments is so different from the normal excitation of the cortex that the experimenters should be much more cautious than they are in explaining cortical function on the basis of what they observe after applying the electrode. Walshe's exposition is clear, and his definition of terms is important. It is the use of ambiguous words that has led to much of the difficulty.

In the second paper<sup>33</sup> he reviews the evidence from animal experiments and from clinical observations and discusses the relation of the pyramidal system to the motor cortex, to the subordinate motor mechanisms and to the musculature. The higher levels of cortex employ the pyramidal system by way of short neurons to the motor area. This mechanism has to do with skilled movements including speech (eupraxia and euphasia). The motor area proper has its outlet directly through the pyramidal system. The cortical neurons are, of course, activated by afferent impulses, so the idea of a motor cortex controlling movement is fundamentally wrong. The masses of afferent impulses from thalamus and cortical sensory areas initiate and control the reactions of the motor cortex. It is a sensorimotor, reflex mechanism. It is closely associated, in both its afferent and its efferent aspects, with the basal ganglions and the cerebellum. Finally it plays on the motor cells of the spinal cord by way of a complex system of associated short neurons in the spinal gray matter. This makes it extremely unlikely that the pyramidal tract normally innervates single muscles. The thesis still holds that the cortex innervates movements and not muscles. In summary Walshe says:

The pyramidal tract is an internuncial path, a common path, standing between the massed receptors on the one hand and the motor mechanisms of the nervous system on the other. It has evolved in particular relation to the development of the distance receptors, perhaps vision alone, and has reached its highest importance in man. It is the path by way of which the distance receptors put the motor mechanisms of the nervous system in operation; activate, and thereafter direct their action throughout the performance of those sequences of willed movement, short and long, simple and complex, characteristic of the normal organism. *The pyramidal system of itself initiates nothing, and to speak of it as*

33. Walshe, F. M. R.: On the Role of the Pyramidal System in Willed Movements, *Brain* 70:329, 1947.

*'responsible for' this or that category of movements is to ignore the course and motive power of its activities. It is simply the channel through which pass the impulse volleys by which willed movement is activated and continuously moulded by controlling cortical afferent patterns of excitation.* If this be so, then it is concerned with all possible willed movements, and all aspects of willed movement, and if, as has been postulated, the cortex by way of the pyramidal system fractionates and then combines the functional elements of reflex segmental mechanisms, then every willed movement, short and long, small and large, restricted and ample, is as wholly pyramidal as it is extrapyramidal, and separate categories of movement thus anatomically classified or grouped as discrete or stereotyped have no existence as phenomena; they are abstractions not discernible as things or events in nature.

Adrian <sup>34</sup> in his Hughlings Jackson lecture draws similar conclusions from an entirely different set of data. From his refined study of nerve impulses, reverberating circuits and rhythmic activity, he comes to the conclusion that any nerve element in the afferent pattern leads to a change of central activity. He says:

Purposive acts must, therefore, be moulded like the movements of walking, by the controlling afferent patterns which are set up as the act progresses. The exciting disturbance may subside owing to fatigue or distraction, anything which will deflect our purpose; but the particular afferent pattern which signals accomplishment, the temporal and spatial distribution of sensory activity, must be uniquely related to the exciting pattern which it can dissipate. It must be in some way the inverse of the exciting pattern, the key that fits that particular lock. If this argument is valid it follows that one clue to the nature of the exciting pattern is to be sought in the nature of the afferent patterns which bring it to an end.

This brings in the important principle of "feed-back," a term borrowed from electrophysics, as are so many of our neurologic similes. In 1943 Rosenblueth, Wiener and Bigelow <sup>35</sup> wrote their classic paper on this subject. They rescued teleology from its scientific unpopularity, arguing that purposeful activity is the most important kind of behavior since it makes room for volition. "Feed-back" is the mechanism that makes this possible. In physiology it means that the behavior is controlled by sensory impulses that come back to the organism as a result of the behavior. "The behavior of an object is controlled by the margin of error at which the object stands, at a given time, with reference to a relatively specific goal. The feed-back signals from the goal are used to restrict outputs which would otherwise go beyond the goal." All purposeful behavior requires this sort of feed-back. It is obviously important in such functions as that of the cerebellum. It is also essential to intelligent behavior at higher levels. Predictive extrapolations

34. Adrian, E. D.: General Principles of Nervous Activity, Brain **70**:1, 1947.

35. Rosenblueth, A.; Wiener, N., and Bigelow, J.: Behavior, Purpose and Teleology, Philos. of Sc. **10**:18, 1943.



would be impossible without it, and these are the basis of intelligence. Thorndike<sup>36</sup> has shown a similar mechanism to be important in learning. It signals back to the brain of the organism the satisfyingness of the reaction which is confirmed or not. Confirmation makes the reaction take place more easily next time. If such neurologic mechanisms can be proved (and the evidence for them is good) science can take a step forward out of its fatalism and make room for such concepts as choice and volition.

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36. Thorndike, E. L.: *Man and His Works*, (William James Lectures, 1942-1943), Cambridge, Mass., Harvard University Press, 1943.

## CARDIOVASCULAR DISEASES

A Review of Significant Publications From January 1944 to June 1947

OGLESBY PAUL, M.D.

With the Editorial Assistance of

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BOSTON

*(Concluded from Page 238)*

### CORONARY HEART DISEASE

The predilection of atherosclerosis for the coronary arteries is the subject of a paper by Dock<sup>126</sup> which provides much food for thought. Dock points out that atheromatosis may be limited to the coronary arteries, without evident involvement of other portions of the vascular system and that this is the rule in coronary heart disease in men under 40. He discusses the role of hypercholesteremia, pointing out that there is a high incidence of coronary artery disease in congenital xanthomatosis and also in other conditions in which there is a high blood cholesterol level, as in obesity, diabetes mellitus and myxedema. He also refers to the possibility that the increased incidence of myocardial infarction in hypertensive persons may be due to the greater oxygen needs of the left ventricle as well as to a greater severity of atherosclerosis. In his studies of the intima of the coronary arteries of newborn infants Dock found that the male begins life with a coronary intima three times as thick as that of the female, this thickening being present only in the epicardial branches of the coronary arteries. He considers the possibility that despite this natural endowment of the male sex no coronary atherosclerosis need occur if no hypertension ensues and if cholesterol metabolism is efficient.

The role of cholesterol in coronary heart disease was investigated by Shaffer,<sup>127</sup> who compared a series of 100 patients with duodenal ulcer (who had been on a diet presumably rich in cholesterol for five or more years) with a group of 500 controls of the same age and sex ratio without known ulcer or endocrinopathy. He noted the same incidence of myocardial infarction (3 per cent) in the two groups and concluded that the role of cholesterol in the pathogenesis of coronary heart disease is doubtful. It should be pointed out that exact information as to the

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126. Dock, W.: The Predilection of Atherosclerosis for the Coronary Arteries, J. A. M. A. **131**:875 (July 13) 1946.

127. Shaffer, C. F.: Nutritional Rôle of Cholesterol in Human Coronary Arteriosclerosis, Ann. Int. Med. **20**:948, 1944.

diet of these two groups was not available. Furthermore, a large oral cholesterol intake does not necessarily produce an increase in the cholesterol deposits in the body, as this compound is broken down in the process of digestion and absorption in the gastrointestinal tract.

Wilens<sup>128</sup> has attacked this problem from a different point of view. He has reviewed the reports of necropsy on 1,250 persons aged 35 or over, using the admittedly rather unreliable estimate of the state of nutrition of the body and of the presence of atherosclerosis as indicated in the protocols. As he points out, loss of weight due to terminal illness tended to reduce rather than exaggerate any differences in the incidence of atherosclerosis which might be related to the original state of nutrition. His statistics reveal that the incidence of atherosclerotic disease was higher in obese persons than in those who were poorly nourished; for example, in 169 obese men the incidence of advanced atherosclerosis was 40 per cent as compared with an incidence of 16 per cent in 367 men who were considered to be poorly nourished. Wilens believes that the frequency of this type of vascular disorder is higher in young obese persons than in old ones and that the relationship between atherosclerosis and the state of nutrition is independent of sex, hypertension, weight of the heart and diabetes.

One may justifiably view with alarm the increasing number of reports of fatal coronary heart disease in young persons. Scott and Miller<sup>129</sup> report a case of fatal coronary thrombosis in an infant 11 months of age, and French and Dock,<sup>130</sup> Poe<sup>131</sup> and Richards<sup>132</sup> report fatal myocardial infarction in persons between the ages of 19 and 40. French and Dock stress the fact that 91 per cent of a group of 80 young soldiers who died of coronary heart disease were overweight. They report that vigorous effort and activity of early morning chores brought on fatal attacks in over 50 per cent of their cases. In this regard Blumgart,<sup>133</sup> citing 11 examples of acute myocardial infarction related to effort, states that the pathologic mechanisms involved may be subintimal hemorrhages, rupture of an atheromatous abscess or relative ischemia brought on by exertion.

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128. Wilens, S. L.: A Study on the Bearing of General Nutritional State to Atherosclerosis, *Arch. Int. Med.* **79**:129 (Feb.) 1947.

129. Scott, E. P., and Miller, A. J.: Coronary Thrombosis: Report of a Case in an Infant Eleven Months of Age, *J. Pediat.* **28**:478, 1946.

130. French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, *J. A. M. A.* **124**:1233 (April 29) 1944.

131. Poe, W. D.: Fatal Coronary Artery Disease in Young Men, *Am. Heart J.* **33**:76, 1947.

132. Richards, G. A.: A Case of Coronary Thrombosis with Myocardial Infarction in a Nineteen Year Old White Male, *Ann. Int. Med.* **24**:908, 1946.

133. Blumgart, H. L.: The Relation of Effort to Attacks of Acute Myocardial Infarction, *J. A. M. A.* **128**:775 (July) 1945.

A comprehensive study of the clinical aspects of pain in the chest has been undertaken by Harrison.<sup>134</sup> An analysis of the symptoms of 77 patients with angina pectoris reveals certain interesting facts. For example, 11 patients who had pain on effort also complained of the same symptom on lying down; in some, swallowing and eating precipitated pain, and relief was at times obtained by the ingestion of food, vomiting, belching or the expulsion of flatus. Spontaneous hypoglycemia, paroxysmal dyspnea and paroxysmal tachycardia were among the initiating nocturnal factors. Harrison refers to apparent recovery from angina pectoris in 12 of his patients, 4 being relieved of their symptoms after a coronary occlusion, 3 after hypoglycemia or anemia had been controlled and 5 without apparent cause (it may be assumed that an adequate collateral circulation had developed). In all, 10 per cent of his patients had anginal pain unrelated to effort. It is, of course, possible that some of the patients whom he describes were suffering either from a condition other than coronary heart disease or from coronary heart disease plus an associated gastrointestinal or other lesion, since pathologic proof of the existence of coronary sclerosis or disease of the aortic valve was not available in the majority of his cases. The same author has considered the problem of pain arising in both the esophagus and the stomach, pointing out that either of these types may mimic angina pectoris even to the radiation of pain to the left shoulder and arm. He calls attention to the fact that nitroglycerin may relieve esophageal and gastric pain, although usually not so effectively as it does in coronary insufficiency. Josey and Murphey<sup>135</sup> remind us that the differential diagnosis of angina pectoris should include rupture of a cervical intervertebral disk.

The use of tests designed to assist in the diagnosis of coronary heart disease has been the subject of numerous papers during recent years. Indeed, it would appear that both the exercise and the anoxemia tests are probably receiving a wider use than is necessary. Master, Huzie, Brown and Parker<sup>136</sup> have compared the "two-step" exercise test with the Levy anoxemia test (which utilizes inhalation of a 10 per cent oxygen and a 90 per cent nitrogen mixture). It is the conclusion of these authors from studies on 84 navy personnel that the results of the two procedures were almost identical. They believe, however, that the anoxemia test is more severe and causes more of a reaction than does the exercise test in addition to being a procedure which requires special

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134. Harrison, T. R.: Clinical Aspects of Pain in the Chest: I. Angina Pectoris, *Am. J. M. Sc.* **207**:561, 1944; II. Pain Arising in the Esophagus, *ibid.* **209**:765, 1945; III, Pain Arising from the Stomach, *ibid.* **209**:771, 1945.

135. Josey, A. I., and Murphey, F.: Ruptured Intervertebral Disk Simulating Angina Pectoris, *J. A. M. A.* **131**:581 (June 15) 1946.

136. Master, A. M.; Huzie, S.; Brown, R. C., and Parker, R. C., Jr.: The Electrocardiogram and the "Two-Step" Exercise, *Am. J. M. Sc.* **207**:435, 1944.

equipment. Biörck<sup>137</sup> in Stockholm has likewise employed both tests and although he believed that the anoxemia test was of greater diagnostic value than was the use of exercise he found that the majority of patients who inhaled the 10 per cent oxygen and 90 per cent nitrogen mixture became cyanotic and that many got a severe headache. He also described shock in 2 cases. It is his conclusion that care must be used in the interpretation of negative reactions to tests.

A study has been reported by Weintraub and Bishop,<sup>138</sup> who used the anoxemia procedure on 200 controls and on 20 patients with known angina pectoris on effort. It was noted that 2 of the patients with coronary heart disease had neither pain nor positive electrocardiographic changes while in the oxygen-poor atmosphere. Of the 200 controls, none had pain but 9 showed electrocardiographic changes. Unpleasant reactions included restlessness, air hunger, headache, pain in the chest and clonic tremors, and of the total 220 patients, 8 had severe reactions. The use of the anoxemia test has also been described by Pruitt, Burchell and Barnes,<sup>139</sup> who list thirty-nine unfavorable reactions in two hundred and eighty-nine tests. Four of their patients temporarily lost consciousness, 9 appeared on the verge of shock and 2 more experienced cardiac arrest for a brief period. The occurrence of pain alone during this test was considered to be an unreliable indication of the presence of coronary heart disease. They state in summary: "Use of the anoxia test should be restricted even among acceptable cases to instances in which (1) serious disagreement regarding diagnosis has occurred, and (2) the establishment of a definite diagnosis is of such importance that acquisition of all helpful evidence is imperative." This view would indeed appear to be a sensible one. The use of low oxygen tests to determine the myocardial reserve of children, as described by Mannheimer,<sup>140</sup> appears to have little to recommend it.

The prognostic significance of auricular fibrillation in association with myocardial infarction was studied at the Los Angeles County General Hospital by Askey and Neurath.<sup>141</sup> They found the mortality among a group of 1,247 patients with myocardial infarction to be 51.5 per cent. The mortality in a group of 84 patients with auricular fibril-

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137. Biörck, G.: Hypoxaemia Tests in Coronary Disease, *Brit. Heart J.* **8**: 17, 1946; Anoxemia and Exercise Tests in the Diagnosis of Coronary Disease, *Am. Heart J.* **32**:689, 1946.

138. Weintraub, H. J., and Bishop, L. F., Jr.: The Anoxemia Test for Coronary Insufficiency, *Ann. Int. Med.* **26**:741, 1947.

139. Pruitt, R. D.; Burchell, H. B., and Barnes, A. R.: The Anoxia Test in the Diagnosis of Coronary Insufficiency: Study of Two Hundred and Eighty-Nine Cases, *J. A. M. A.* **128**:839 (July 21) 1945.

140. Mannheimer, E.: The Hypoxia Tolerance Test of the Heart in Children, *J. Pediat.* **29**:329, 1946.

141. Askey, J. M., and Neurath, O.: The Prognostic Significance of Auricular Fibrillation in Association with Myocardial Infarction, *Am. Heart J.* **29**:575, 1945.

lation (selected from the same series) was 79.8 per cent, however, and the percentage of deaths was even higher when the arrhythmia preceded the infarction; the mortality was likewise higher with persistent fibrillation than with transient fibrillation.

As with congestive heart failure, there has been interest in the necessity for restriction of activity and the effect on the recovery rate and on the healing process in the treatment of myocardial infarction. Using rats as their experimental animals, Thomas and Harrison<sup>142</sup> produced an area of myocardial damage on the left ventricular surface by actual searing of the muscle. They then divided their animals into several groups; one of the groups exercised as desired, the second were given the optional use of a treadmill, the third were made to take exercise (swimming) and the fourth had their activity restricted by snug-fitting cages. Of 49 rats whose activity was limited, 34 died at the end of three months (the immediate postoperative deaths are excluded); only 18 of 47 animals who exercised as they desired died. There was no evidence that animals forced to exercise did well or, indeed, poorly as a group. While the authors recognize that such experimental data may have a limited application to clinical problems, they suggest that strict rest in bed for the first two weeks of recovery from infarction may be all that is desired. They did observe that when cardiac rupture occurred in their animals it came usually during the second week. Of great significance in this respect is the work of Friedman and White,<sup>143</sup> and that of Jetter and White,<sup>144</sup> who found an incidence of rupture in the heart of only 9 per cent in 105 patients with acute myocardial infarction studied pathologically at the Massachusetts General Hospital and an incidence of 73 per cent among 22 patients with acute infarction studied pathologically in Massachusetts mental institutions. In the latter group restriction of activity had not been employed because of the obvious difficulties in diagnosis. It was found that death always ensued rapidly after the episode of rupture and that all deaths occurred within two weeks of the onset of infarction. No healed infarcts were found to have ruptured. Certainly these statistics point to the wisdom of at least a fortnight's rest in bed after myocardial infarction.

The question of the use of anticoagulants in the treatment of coronary heart disease is a matter of recent investigation. Meyers and Poindexter<sup>145</sup> have found that the prothrombin time appears to shorten

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142. Thomas, W. C., and Harrison, T. R.: The Effect of Artificial Restriction Of Activity on the Recovery of Rats from Experimental Myocardial Injury, *Am. J. M. Sc.* **208**:436, 1944.

143. Friedman, S., and White, P. D.: Rupture of the Heart in Myocardial Infarction: Experience in a Large General Hospital, *Ann. Int. Med.* **21**:778, 1944.

144. Jetter, W. W., and White, P. D.: Rupture of the Heart in Patients in Mental Institutions, *Ann. Int. Med.* **21**:783, 1944.

145. Meyers, L., and Poindexter, C. A.: A Study of the Prothrombin Time in Normal Subjects and in Patients with Arteriosclerosis, *Am. Heart J.* **31**:27, 1946.

nocturnally in patients with coronary artery disease (they studied only 6 normal controls and 10 patients with coronary heart disease). These authors also found a definite trend toward shortening of prothrombin time in 13 patients with acute coronary occlusion and noted that this change preceded the use of digitalis (which was employed in 5 cases) and that the abnormality lasted for several weeks. The test which they employed made use of both diluted and undiluted plasma. Similar studies, using the heparin-retarded clotting test in patients suffering from acute coronary thrombosis, have been reported by Ogura and his associates.<sup>146</sup> While conceding that the laboratory evidence which they obtained was not an infallible guide, they concluded that an acceleration of the blood coagulation occurred usually by the second or third day in 78 per cent of 27 cases so studied and lasted to about the seventeenth day. Reviewing the incidence of embolic or thrombotic processes during the immediate convalescence from acute myocardial infarction, Nay and Barnes<sup>147</sup> found that in 100 such patients (none of whom received anticoagulants) there were episodes of a second myocardial infarction in 15, episodes of pulmonary embolism in 14, cerebrovascular accidents in 8, thrombophlebitis in 7 and peripheral arterial occlusion in 4.

These investigations have naturally led to the use in certain clinics of anticoagulants in the treatment of acute coronary heart disease. Wright<sup>148</sup> has reported on the use of "dicumarol" in 76 patients with coronary thrombosis who had had multiple thrombi or repeated embolic phenomena and in 33 patients with uncomplicated coronary thrombosis. In his series 15 patients succumbed, 11 from heart failure and 4 as a direct, immediate result of the "insult of thrombosis." It is his belief that "dicumarol" is of value in the prevention of these complications which Nay and Barnes described, and he advises its use for thirty days after the last episode of thrombosis or embolism. In his series there were no serious toxic results from the use of the drug, but he stresses the fact that the prothrombin level must be determined before the daily dose of the drug is administered. Peters, Guyther and Brambel<sup>149</sup> and Nichol and Page<sup>150</sup> have similarly been encouraged

146. Ogura, J. H.; Fetter, N. R.; Blankenhorn, M. A., and Glueck, H. I.: Changes in Blood Coagulation Following Coronary Thrombosis Measured by the Heparin Retarded Clotting Test (Waugh and Ruddick Test), *J. Clin. Investigation* **25**:586, 1946.

147. Nay, R. M., and Barnes, A. R.: Incidence of Embolic or Thrombotic Processes During the Immediate Convalescence from Acute Myocardial Infarction, *Am. Heart J.* **30**:65, 1945.

148. Wright, I. S.: Experiences with Dicumarol (3, 3' Methylene-Bis-[4-Hydroxycoumarin]) in the Treatment of Coronary Thrombosis with Myocardial Infarction, *Am. Heart J.* **32**:20, 1946.

149. Peters, H. R.; Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, *J. A. M. A.* **130**:398 (Feb. 16) 1946.

150. Nichol, E. S., and Page, S. W.: Dicumarol Therapy in Acute Coronary Thrombosis, *J. Florida M. A.* **32**:365, 1946.

by their results with this form of treatment in acute coronary heart disease. Nichol<sup>151</sup> does, however, refer to 1 patient who died from a cerebral hemorrhage, attributable probably to the "dicumarol." These reports are of great interest, but still further work is required before the general use of anticoagulants in this type of heart disease can be recommended. It should be emphasized once again that careful laboratory observation of the prothrombin level is essential.

Brief mention may be made of recent reports on the use of certain other drugs in coronary artery disease. Mokotoff and Katz<sup>152</sup> studied the hearts of a series of 46 dogs in which the left anterior descending coronary artery had been ligated eight weeks previously. Subsequently they had treated one third of the animals with aminophylline and one third with papaverine hydrochloride, and the remaining third had been kept as controls. These investigators noted that the hearts of the dogs who had received either of the two drugs employed showed smaller infarcts than did the hearts of the control group. Papaverine hydrochloride seemed to be somewhat superior to aminophylline in this regard. Riseman and his associates<sup>153</sup> have appraised the value of alcohol, papaverine hydrochloride and cobra venom in patients with angina pectoris who were subjected to a standardized exercise tolerance test. Their results indicated that alcohol was of relatively little value except to promote a sense of well-being and that papaverine hydrochloride given intravenously had a definite but brief beneficial effect (oral administration was ineffective) but that cobra venom given intramuscularly was of distinct benefit in 7 of 12 patients with angina pectoris and, in particular, in 4 of 5 patients who did not respond to conventional therapy. They also observed that papaverine hydrochloride given by the intravenous route afforded considerable relief of pain when myocardial infarction was present.

Proger and Dekaneas<sup>154</sup> have endeavored to combat myocardial anoxia by enhancing the tissue uptake of oxygen by the intravenous use of cytochrome C. In a small group of cases of coronary heart disease they found that this drug could prevent the appearance of electrocardio-

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151. Nichol, E. S.: Treatment of Acute Coronary Thrombosis with Dicumarol: Further Observations, *Am. Heart J.* **33**:722, 1947.

152. Mokotoff, R., and Katz, L. N.: The Effect of Theophyllin with Ethylenediamine (Aminophylline) and of Papaverine Hydrochloride on Experimental Myocardial Infarction in the Dog, *Am. Heart J.* **30**:215, 1945.

153. Gray, W.; Riseman, J. E. F., and Stearns, S.: Papaverine in the Treatment of Coronary Artery Disease, *New England J. Med.* **232**:389, 1945. Freedberg, A. S., and Riseman, J. E. F.: Cobra Venom in the Treatment of Angina Pectoris, *ibid.* **233**:462, 1945. Stearns, S.; Riseman, J. E. F., and Gray, W.: Alcohol in the Treatment of Angina Pectoris, *ibid.* **234**:578, 1946.

154. Proger, S., and Dekaneas, D.: Some Effects of Injected Cytochrome C in Myocardial and Cerebral Anoxia in Man, *J. Pediat.* **29**:729, 1946.



graphic changes accompanying the Levy anoxemia test for coronary insufficiency. The preparation did not appear to be more than moderately effective in increasing capacity for physical exertion in patients with angina pectoris, however, and had no effect in acute myocardial infarction. It is not surprising that the consequences of a "medical thyroidectomy" by the use of thiouracil in patients with coronary heart disease should be the subject of several reports in view of earlier enthusiasm for surgical ablation of the thyroid gland. Raab<sup>155</sup> was impressed with the beneficial effects of thiouracil in 10 patients with angina, and Ben-Asher<sup>156</sup> concluded that 67 per cent of a series of 37 of his patients were improved by its administration. DiPalma and MaGovern,<sup>157</sup> on the other hand, were disappointed in its use and described the disadvantages attending prolonged ingestion of the drug. In view of the spontaneous remissions which are known to occur with angina pectoris and the lack of adequate controls in the series just mentioned as well as the previous unfavorable experiences with surgical thyroidectomy, it would appear that thiouracil has little place in the armamentarium employed routinely in the therapy of coronary heart disease. Further studies<sup>158</sup> on the use of testosterone in angina pectoris have likewise failed to confirm the value of this hormonal preparation, and vitamin E, the use of which has received considerable premature publicity, has been the subject of a recent sobering editorial<sup>159</sup> which points to the need of further careful evaluation.

Finally, reference should be made to surgical measures which have been described for the relief of intractable coronary pain. White,<sup>160</sup> in summarizing his experiences with paravertebral injection of alcohol in the upper thoracic sympathetic ganglions, has reported excellent results in 56 per cent and 8 operative deaths in 8 per cent of 75 cases; post-operative intercostal neuralgia was a serious complaint in 10 per cent of the series. Of another group of 8 patients who were subjected to sympathectomy performed in the upper thoracic area, 4 were described as having excellent relief for more than one year and 3 others did well temporarily until their demise within twelve months of operation. The

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155. Raab, W.: Thiouracil Treatment of Angina Pectoris: Rationale and Results, *J. A. M. A.* **128**:249 (May 26) 1945.

156. Ben-Asher, S.: Further Observations on the Treatment of the Anginal Syndrome with Thiouracil, *Am. Heart J.* **33**:490, 1947.

157. DiPalma, J. R., and MaGovern, J. J.: Disadvantages of Thiouracil Treatment of Angina Pectoris, *Am. Heart J.* **32**:494, 1946.

158. Levine, E. B., and Sellers, A. L.: Testosterone in Angina Pectoris, *Am. J. M. Sc.* **212**:7, 1946.

159. Vitamin E and Heart Disease, Current Comment, *J. A. M. A.* **131**:746 (June 29) 1946.

160. White, J. C.: The Surgical Relief of Severe Angina Pectoris, *Bull. New England M. Center* **9**:1, 1947.

relief of angina by the drastic procedure of pericoronary neurectomy combined with ligation of the great cardiac vein has been reported by Fauteux as successful in 1 patient.<sup>161</sup> Of 10 other patients for whom surgical treatment was limited to ligation of the great cardiac vein, 7 received some benefit and 1 died.

#### PULMONARY HEART DISEASE

The recording of the pressure of the right side of the heart in patients with chronic pulmonary disease has been accomplished by Bloomfield,<sup>162</sup> working with Cournand and his associates. By means of cardiac catheterization the authors demonstrated that an extreme degree of pulmonary emphysema or fibrosis might exist with little if any evidence of strain on the right side of the heart as revealed by this technic. The whole subject of chronic cor pulmonale has been reviewed by Spain and Handler,<sup>163</sup> who studied 60 cases from the files of the Bellevue Hospital in New York city. After summarizing the clinical features in this group of cases, these writers concluded that the primary cause of cor pulmonale was not obliteration of the pulmonary vascular bed, fibrosis of the lungs or the influence of polycythemia but rather the result of the changed pressure relation within the alveoli producing an increased resistance to the flow of blood. They point out that the term emphysema does not necessarily imply an associated pulmonary fibrosis.

The interesting condition of thrombosis of the pulmonary veins has been discussed by Spain and Moses.<sup>164</sup> These authors recorded 15 cases in which there was associated embolism to the arterial system, including the kidneys and the spleen. Twelve of the patients showed extensive pulmonary tuberculosis, for 1 the diagnosis of bronchiogenic carcinoma was made, 1 had bronchiectasis and only 1 showed no pathologic changes other than pulmonary infarction.

It is not the function of this review to discuss peripheral vascular disease. Mention should be made, however, of the recent extensive literature relating to venous thrombosis and pulmonary embolism since

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161. Fauteux, M.: Treatment of Coronary Disease with Angina by Pericoronary Neurectomy Combined with Ligation of the Great Cardiac Vein, *Am. Heart J.* **31**:260, 1946.

162. Bloomfield, R. A.; Lauson, H. D.; Cournand, A.; Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients with Chronic Pulmonary Disease and Various Types of Cardio-circulatory Disease, *J. Clin. Investigation* **25**:639, 1946.

163. Spain, D. M., and Handler, B. J.: Chronic Cor Pulmonale: Sixty Cases Studied at Necropsy, *Arch. Int. Med.* **77**:37 (Jan.) 1946.

164. Spain, D. M., and Moses, J. B.: Thrombosis and Embolism of Pulmonary Vessels with Special Reference to Pulmonary Vein Thrombosis, *Am. J. M. Sc.* **212**:707, 1946.

this condition is frequently encountered in patients with cardiac disease. As Carlotti and his associates<sup>165</sup> have pointed out, there is actually a greater incidence of pulmonary embolism among medical patients than among surgical patients, with the majority of the former suffering from heart disease. There is some difference of opinion as to the best form of treatment for the patient who exhibits either phlebothrombosis or thrombophlebitis. Allen, Linton and Donaldson<sup>166</sup> recommend ligation of the superficial femoral veins bilaterally as the treatment of choice in established phlebothrombosis and in early thrombophlebitis, and they also suggest the wisdom of prophylactic ligation of the veins in aged and debilitated patients. Ochsner<sup>167</sup> agrees that surgical intervention is indicated when phlebothrombosis is present but states that venous ligation is rarely necessary in the treatment of uncomplicated thrombophlebitis. The use of anticoagulants instead of surgical measures has been advocated by several writers. Heparin has been recommended by Loewe and Hirsch<sup>168</sup> and by Bauer<sup>169</sup> as being an effective form of therapy in the presence of venous thromboembolic disease, and the combined use of heparin and "dicumarol" or use of the latter alone has been described by Allen,<sup>170</sup> of the Mayo Clinic, and others. The statistics which these various writers have published can be obtained from their original articles, but it is perhaps fair to say that good results appear to have been secured both by surgical treatment and by the use of anticoagulants.

Two further reports<sup>171</sup> of fatalities resulting from the administration of morphine to patients with kyphoscoliosis and kyphoscoliotic heart disease call attention once again to the lethal effects of even minute doses of this drug when an extremely reduced pulmonary reserve is present. The conclusion that morphine is contraindicated in this condition (as are all narcotics) may also be applied to severe chronic pulmonary disease in general.

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165. Carlotti, J.; Hardy, I. B., Jr.; Linton, R. R., and White, P. D.: Pulmonary Embolism in Medical Patients, *Am. Heart J.* **33**:737, 1947.

166. Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism, *J. A. M. A.* **133**:1268 (April 26) 1947.

167. Ochsner, A.: Venous Thrombosis, *J. A. M. A.* **132**:827 (Dec. 7) 1946.

168. Loewe, L., and Hirsch, E.: Heparin in the Treatment of Thromboembolic Disease, *J. A. M. A.* **133**:1263 (April 26) 1947.

169. Bauer, G.: Heparin Therapy in Acute Deep Venous Thrombosis, *J. A. M. A.* **131**:196 (May 18) 1946.

170. Allen, E. V.: The Clinical Use of Anticoagulants: Report of Treatment with Dicumarol in 1,686 Postoperative Cases, *J. A. M. A.* **134**:323 (May 24) 1947.

171. Daley, R.: Morphine Hypersensitivity in Kyphoscoliosis, *Brit. Heart J.* **7**:101, 1945. Katz, K. H., and Chandler, H.: Morphine Hypersensitivity in Kyphoscoliotic Heart Disease. read at meeting of New England Heart Association, January 1946.

## OTHER CARDIOVASCULAR CONDITIONS

While the treatment of cardiovascular syphilis with penicillin has been introduced too recently for a seasoned evaluation comparable to that made after experience over several decades with iodides, bismuth and arsenicals, it is nevertheless of interest to review those cases of cardiovascular syphilis in which the new form of therapy has been used. Russek, Cutler, Fromer and Zohman<sup>172</sup> treated 15 patients with syphilitic aortitis (4 of them with aneurysms) on a dose schedule of 40,000 units of penicillin intramuscularly every two hours until a total of 3,400,000 units had been given. The authors state that 4 of their patients showed definite improvement and that only 1 experienced mild substernal pain. No serious toxic reactions occurred.

Among descriptions of still other diseases which are found to affect the heart, Gore<sup>173</sup> has reviewed 1,402 cases of myocarditis recorded at the Army Institute of Pathology during World War II and has listed myocardial involvement associated with syphilis, scarlet fever, diphtheria, acute meningococcemia, scrub typhus, tuberculosis, epidemic hepatitis and many other diseases.<sup>174</sup> An excellent study of 2 patients who succumbed to acute myocarditis due to infection with influenza A has been reported by Finland and his colleagues,<sup>175</sup> and fatalities from cardiac disease secondary to cutaneous diphtheria have been described by Kay and Livingood<sup>176</sup> and by Solomon and Irwin.<sup>177</sup> Other writers<sup>178</sup> have described meningococcic myocarditis and myocarditis in children associated with acute laryngotracheobronchitis. Electrocardiographic evidence of cardiac complications in infectious mononucleosis has been reported by Evans and Graybiel<sup>179</sup> and in mumps by Wendkos and

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172. Russek, H. I.; Cutler, J. C.; Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis with Penicillin, *Ann. Int. Med.* **25**:957, 1946.

173. Gore, I.: Myocarditis in Infectious Diseases, *Am. Pract.* **1**:292, 1947.

174. Seventy per cent of the patients who died from syphilis or from scarlet fever showed demonstrable myocarditis, and myocarditis was found in 100 per cent of the cases of acute meningococcemia and scrub typhus.

175. Finland, M.; Parker, F., Jr.; Barnes, M. W., and Joliffe, L. S.: Acute Myocarditis in Influenza A Infections, *Am. J. M. Sc.* **209**:455, 1945.

176. Kay, C. F., and Livingood, C. S.: Myocardial Complications of Cutaneous Diphtheria, *Am. Heart J.* **31**:744, 1946.

177. Solomon, S., and Irwin, C. W.: Cutaneous Diphtheria with Toxic Myocarditis: Report of a Fatal Case with Necropsy Findings, *Ann. Int. Med.* **26**: 116, 1947.

178. Holman, D. V., and Angevine, D. M.: Meningococcus Myocarditis, *Am. J. M. Sc.* **211**:129, 1946. Saphir, O.: Laryngeal Edema, Myocarditis and Unexpected Death (Early Acute Laryngotracheobronchitis), *ibid.* **210**:296, 1945.

179. Evans, W. F., and Graybiel, A.: Electrocardiographic Evidence of Cardiac Complications in Infectious Mononucleosis, *Am. J. M. Sc.* **211**:220, 1946.

Noll,<sup>180</sup> and abnormalities of the electrocardiogram occurring during pneumococcic pneumonia have been summarized by Thomson and his associates.<sup>181</sup> The importance of the myocardial involvement in South American trypanosomiasis (Chagas' disease) has been well indicated by Moseley and Miller<sup>182</sup> in a recent review of this disease. Most physicians who live in North America are little aware of the frequency and severity of the cardiac involvement in this interesting condition which may closely simulate coronary heart disease both in its symptoms and in its electrocardiographic changes.

Finally, mention should be made of the report by Levy and von Glahn<sup>183</sup> of a group of 10 patients with cardiac hypertrophy of unknown cause. Their series adds 10 more cases to those described by other writers during the past four years. Although it does not throw further light on the etiology of this mysterious disease, it presents a good summary of the clinical and pathologic findings. It is of interest that 2 of their patients had positive Wassermann reactions. These authors found that arterial embolism from mural thrombi was a frequent occurrence, the lungs being involved six times, the kidneys four times and the spleen and the retina once each. All their patients died, 7 from progressive myocardial insufficiency and the remaining 3 from sudden death attributable to heart disease. In no instance was there evidence of avitaminosis. At autopsy the coronary arteries showed a striking absence of advanced sclerosis; myocardial hypertrophy was invariably present (with associated necrosis and fibrosis in 4 of the cases), and mural thrombi were present in 6 instances. The valves of the heart were normal.

Fletcher<sup>184</sup> has studied the cardiac output in a case of pericardial effusion and has found that despite the presence of cardiac tamponade the effective right auricular filling pressure and the cardiac output were within normal limits. He suggests that it may be only in the agonal stage of tamponade that the pericardial pressure approaches the venous pressure and the cardiac output falls. Changes in the circulation in constrictive pericarditis have been investigated by Lyons and Burwell,<sup>185</sup>

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180. Wendkos, M. H., and Noll, J.: Myocarditis Caused by Epidemic Parotitis, *Am. Heart J.* **27**:414, 1944.

181. Thomson, K. J.; Rutstein, D. D.; Tolmach, D. M., and Walker, W. H.: Electrocardiographic Studies During and After *Pneumococcus Pneumonia*, *Am. Heart J.* **31**:565, 1946.

182. Moseley, V., and Miller, H.: South American Trypanosomiasis (Chagas' Disease), *Arch. Int. Med.* **76**:219 (Oct.) 1945.

183. Levy, R. L., and von Glahn, W. C.: Cardiac Hypertrophy of Unknown Cause, *Am. Heart J.* **28**:714, 1944.

184. Fletcher, C. M.: Cardiac Output in a Case of Pericardial Effusion, *Brit. Heart J.* **7**:143, 1945.

185. Lyons, R. H., and Burwell, C. S.: Induced Changes in the Circulation in Constrictive Pericarditis, *Brit. Heart J.* **8**:33, 1946.

who have stated the belief that the principal circulatory defect is limitation of the diastolic filling of the ventricles, which results in a diminished output per beat. Unlike the normal heart, the heart with a constricting pericardium fails to increase its output per beat or its rate in the presence of a spontaneous or an induced rise in venous pressure. They noted that spontaneous increases in rate were associated with a reduced output per beat but with a slight increase in the total output per minute. Zimmerman and Durgin<sup>186</sup> have reported on a 27 year old Negro with septicemia and pericarditis caused by *Staphylococcus aureus* who had been treated with sulfadiazine without benefit. The authors then administered 10,000 units of penicillin intrapericardially, giving the drug intramuscularly and intravenously as well, with excellent clinical results and eventual cure.

The effect of posture on the auriculoventricular conduction time has been the subject of three reports. Holmes and Weill<sup>187</sup> have described 2 patients whose P-R interval became prolonged when they were recumbent; the interval returned to normal with a change to the erect position. Four of 20 patients with defective auriculoventricular conduction studied by Manning and Stewart<sup>188</sup> were similarly affected by changes in posture, and Stein<sup>189</sup> has reported a case in which the patient had complete heart block when recumbent and high grade first degree block when sitting. The treatment of 8 patients with ventricular tachycardia with large doses of quinidine sulfate has been reviewed by Zimmerman.<sup>190</sup> Seven of his patients recovered, and 1 died from a massive anterior myocardial infarction. This author disregarded toxicity from quinidine as evidenced by prolongation of the intraventricular conduction time, believing that the use of the drug is essential despite such a finding.

Askey<sup>191</sup> has collected the clinical data on 7 patients in whom hemiplegia developed after stimulation of the carotid sinus. It was of interest that no patient was under 42 years of age and that the hemiplegia was invariably on the side opposite to that on which pressure had been exerted; the neurologic damage was transient or minimal in

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186. Zimmerman, J. J., and Durgin, B.: *Staphylococcus Aureus* Septicemia and Pericarditis Treated with Penicillin, *Am. Heart J.* **31**:93, 1946.

187. Holmes, J. H., and Weill, D. R., Jr.: Incomplete Heart Block Produced by Changes in Posture, *Am. Heart J.* **30**:291, 1945.

188. Manning, G. W., and Stewart, C. B.: Alteration in P-R Interval Associated with Change in Posture, *Am. Heart J.* **30**:109, 1945.

189. Stein, I.: Postural Heart Block, *Am. J. M. Sc.* **212**:604, 1946.

190. Zimmerman, S. L.: Ventricular Tachycardia—A Report of Ten Cases, Eight of Which Were Treated with Quinidine with Recovery in Seven, *Ann. Int. Med.* **23**:634, 1945.

191. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, *Am. Heart J.* **31**:131, 1946.

all cases. He advises that considerable caution be exercised in the use of stimulation of the carotid sinus in elderly or middle-aged persons. The whole subject of the hyperactive cardioinhibitory carotid sinus reflex has been reviewed by Nathanson,<sup>192</sup> who calls attention to the fact that over 65 per cent of 115 patients who demonstrated this condition had no related symptoms. For those persons who have characteristic complaints Nathanson suggests that an increase in pressure within the carotid sinus may be more important as a stimulus than the external pressure as suggested by others. He postulates that a hypersensitivity of the vagus nerve may exist to explain in part some of the failures to relieve the carotid sinus syndrome by surgical denervation, the vagus nerve presumably being reflexly activated by stimuli from other sensory areas in the body.

#### ELECTROCARDIOGRAPHY AND ROENTGENOLOGY

The brisk disagreement regarding the validity of the Einthoven triangle hypothesis continues to flourish in medical literature. Adequate discussion of this and of other complex electrophysical problems must be left to the select few who are competent to argue in this most interesting but special field, and it will suffice here to say that Wolferth and Livezey<sup>193</sup> consider that the Einthoven hypothesis is subject to "enormous error," whereas Wilson and his group<sup>194</sup> and Goldberger<sup>195</sup> too, uphold the validity of the Einthoven concept. Wilson's remarks are buttressed by a wealth of technical knowledge as well as by experimental data, as is apparent to those who peruse his publications. The use of unipolar leads also is a bone of contention between these two groups, but there would appear to be little doubt that the Wilson central terminal, with which unipolar chest and limb leads can be taken, not only offers a happy solution in the choice of precordial leads but also makes available through the unipolar limb leads a new source of electrocardiographic information.

The broad range of the normal in electrocardiography has been illustrated by studies made on healthy young aviators during the recent

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192. Nathanson, M. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex, *Arch. Int. Med.* **77**:491 (May) 1946.

193. Wolferth, C. C., and Livezey, M. M.: A Study of Methods of Making So-Called Unipolar Electrocardiograms, *Am. Heart J.* **27**:764, 1944.

194. Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, *Am. Heart J.* **32**: 277, 1946.

195. Goldberger, E.: The Validity of the Einthoven Triangle Hypothesis, *Am. Heart J.* **29**:369, 1945.

war. Graybiel, McFarland, Gates and Webster<sup>196</sup> reviewed the electrocardiograms of 1,000 aviators; they noted sixteen examples of prolongation of the P-R interval beyond 0.20 second (the longest being 0.28 second) and thirty-eight examples of a QRS interval longer than 0.10 second (the longest being 0.14 second). They also describe in 1 instance a heart rate of 38. "Even after rejecting as frankly abnormal some of the extreme values observed," they state, "it is apparent that the 'normal' extends well into what has commonly been regarded as the abnormal range." Similar conclusions have been reached by Stewart and Manning<sup>197</sup> in an analysis of the electrocardiograms of 500 Canadian airmen. These papers call attention once again to the need for conservatism in the interpretation of borderline electrocardiographic abnormalities, particularly when clinical evidence of heart disease is lacking.

Goldberger<sup>198</sup> has presented a discussion of the differentiation between normal and abnormal Q waves, describing the nature and course of the spread of electrical activity over certain portions of the heart muscle which results in the appearance of Q waves in the electrocardiogram. He refers to the useful concept that the area of infarction in the myocardium acts like a window in the ventricular wall which transmits to the chest wall and the limbs the variations in potential taking place within the ventricular cavity. Both Goldberger and Myers and Oren<sup>199</sup> have stressed the value of the unipolar lead in the left leg in the differentiation of normal from abnormal Q waves from limb lead III. It has been demonstrated in the past by Wilson that the region of a posterior myocardial infarction usually points to the left leg; hence the unipolar lead from the left leg may show a deep or broad Q wave when this condition is present. As these authors point out, it is sometimes possible to distinguish this Q<sub>s</sub> pattern from that due to a transverse position of the heart by the findings in the unipolar leads from both the left arm and the left leg. Such a use of unipolar leads illustrates their practical clinical value.

The significance of marked left axis deviation in the electrocardiogram has been studied critically by Faulkner and Duncan,<sup>200</sup> who

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196. Graybiel, A.; McFarland, R. A.; Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained from One Thousand Young Healthy Aviators, *Am. Heart J.* **27**:524, 1944.

197. Stewart, C. B., and Manning, G. W.: A Detailed Analysis of the Electrocardiograms of Five Hundred R. C. A. F. Aircrew, *Am. Heart J.* **27**:502, 1944.

198. Goldberger, E.: Differentiation of Normal from Abnormal Q Waves, *Am. Heart J.* **30**:341, 1945.

199. Myers, G. B., and Oren, B. G.: Use of the Augmented Unipolar Left Leg Lead in the Differentiation of the Normal from Abnormal Q Wave in Standard Lead III, *Am. Heart J.* **29**:708, 1945.

200. Faulkner, J. M., and Duncan, C. N.: The Significance of Marked Left Axis Deviation in the Electrocardiogram, *Am. J. M. Sc.* **208**:205, 1944.



analyzed two hundred tracings in which  $S_2$  was greater than  $R_2$ . Autopsy reports in 27 of the 200 cases were reviewed, as were the roentgenograms of the chest obtained in 97. These authors noted that the cardiac measurements were within the normal range in 37 per cent of those patients for whom the roentgenograms of the chest were available and that the heart was normal in 30 per cent of the autopsies. They concluded that left axis deviation of considerable degree when present in an otherwise normal tracing is to be regarded as a normal variation.

Wilson and his colleagues<sup>201</sup> have published a comprehensive report on the precordial electrocardiogram (recorded by means of the central terminal). In this paper the authors describe prominence of the R wave over the left side of the precordium associated with abnormal left ventricular preponderance and also refer to unusual prominence of R waves over the right side of the precordium (with relatively small R waves near the apex) in right ventricular hypertrophy. The patterns of right and left bundle branch block as illustrated by changes in the chest leads are discussed as are the abnormalities found in myocardial infarction; the writers refer to the fact that an anteroseptal infarct produces maximal abnormalities in  $V_2$ ,  $V_3$ ,  $V_4$ , whereas an anterolateral infarct is best diagnosed from leads  $V_4$ ,  $V_5$ ,  $V_6$ . They also show that posterior myocardial infarction may at times produce a depression of the S-T segments in the precordial leads, with subsequent prominence of the R and T waves, notably in leads  $V_1$  and  $V_2$ . In a further report Wilson's group<sup>202</sup> has stressed the value of chest leads taken in the fourth, third and even second interspaces in locating high lateral areas of myocardial damage.

The juvenile and adult types of precordial electrocardiographic patterns have been analyzed by Battro and Mendy,<sup>203</sup> who found that negative or diphasic T waves in all the chest leads are common in infancy and that by the tenth year the T waves have usually become upright in leads  $V_5$  and  $V_6$ . A similar report by Suarez and Suarez,<sup>204</sup> based on the precordial tracings of 161 healthy Puerto Ricans, states that a negative T wave in lead  $V_1$  is normal regardless of age or sex but that negativity of the T waves in leads  $V_2$  through  $V_6$  is probably abnormal

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201. Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F.; Erlanger, H.; Kossmann, C. E.; Hecht, H.; Cotrim, N.; de Oliveira, R. M.; Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *Am. Heart J.* **27**:19, 1944.

202. Rosenbaum, F. F.; Wilson, F. N., and Johnston, F. D.: The Precordial Electrocardiogram in High Lateral Myocardial Infarction, *Am. Heart J.* **32**:135, 1946.

203. Battro, A., and Mendy, J. C.: Precordial Leads in Children, *Arch. Int. Med.* **78**:31 (July) 1946.

204. Suarez, R. M., and Suarez, R. M., Jr.: The T Wave of the Precordial Electrocardiogram at Different Age Levels, *Am. Heart J.* **32**:480, 1946.

in males who have reached the age of 19 although in adult females inversion of the T waves in leads  $V_2$  and  $V_3$  is normal.

Using dogs as their experimental animals, Bayley, LaDue and York<sup>205</sup> produced local ventricular ischemia and injury by temporary occlusion of a coronary artery while a continuous electrocardiographic tracing was being obtained directly from the ventricular surface. They observed an initial and extremely transient deep inversion of the T wave followed by what is usually considered to be the earliest change under such conditions, namely, elevation of the S-T segment. The authors believe, therefore, that this ischemic T wave pattern both initiates and concludes the pattern of myocardial infarction. Bayley<sup>206</sup> has also described an electrocardiogram taken during the illness of a 44 year old woman, whose heart at postmortem examination showed unexplained necrosis of the inner half of the wall of the left ventricle. It was notable that the electrocardiogram showed a depression of the S-T segments in leads I, II and  $CF_4$ , a phenomenon which Bayley characterizes as "an injury effect against the rule," which is just the reverse of what is seen with acute diffuse pericarditis. Pardee and Goldenberg,<sup>207</sup> in commenting on incomplete mural myocardial infarcts, have also called attention to the frequency of depression of the S-T segment and inversion of the T wave, similar to that appearing after exercise and anoxemia. This pattern is strikingly similar to the one reported by Bayley. Pardee and Goldenberg believe, however, that while these changes may be similar to those in coronary insufficiency the abnormalities are rarely found in both the limb leads and lead 4F.

The effect of stimulation of the carotid sinus, at times reenforced by an intramuscular injection of neostigmine, on the P-R interval in 16 patients with acute rheumatic fever has been studied by Gubner, Szucs and Ungerleider.<sup>208</sup> These workers obtained a definite prolongation of the P-R conduction time in 12 of the 16 cases; there was no significant lengthening in 16 normal controls. They determined the fact that neostigmine did not in itself prolong the P-R interval and that the effect which they had produced could be abolished by the administration of atropine. It is their suggestion that the mechanism of the auriculo-

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205. Bayley, R. H.; LaDue, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, *Am. Heart J.* **27**:164, 1944.

206. Bayley, R. H.: The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle, *Am. Heart J.* **31**:677, 1946.

207. Pardee, H. E. B., and Goldenberg, M.: Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement, *Am. Heart J.* **30**:367, 1945.

208. Gubner, R.; Szucs, M., and Ungerleider, H. E.: Provocative Prolongation of the P-R Interval in Rheumatic Fever, *Am. J. M. Sc.* **209**:469, 1945.

ventricular block may be an inflammatory process with vascular change in the conduction system which lowers the  $p_H$  in that area, interferes with tissue nutrition and thus inhibits choline esterase, allowing a potentiated vagal effect. Also working with patients with rheumatic carditis, Taran and Szilagyi<sup>209</sup> have elaborated on the thesis that the duration of electrical systole as measured by the Q-T interval is significantly prolonged in all cases of acute rheumatic myocarditis. Although these writers have published considerable statistical information to substantiate their belief, it remains to be seen whether this measurement will be sufficiently valid to justify its routine use. It appears that when these authors measure the Q-T interval to within 0.0001 second they convey an unjustified impression of extraordinary accuracy.

Mention should also be made of human endocardiac electrocardiography, accomplished by placing a catheter with an electrode at its tip in the chambers of the right side of the heart. Battro and Bidoggia<sup>210</sup> have published tracings recorded from the right auricle and ventricle which are of particular interest to those concerned with the process by which the wave of electrical activity proceeds through the myocardium during electrical systole and during the recovery phase.

Chavez, Dorbecker and Celis<sup>211</sup> have reproduced striking angiocardigrams which they obtained by the injection of "diodrast" through a rubber catheter inserted into the external jugular vein, and they demonstrated the undoubted clinical value of this method in the diagnosis of congenital heart disease. It is unlikely, however, that this rather formidable procedure will have more than a limited use at the present time.

#### DRUGS

The pharmacologic basis of cardiac therapy is the subject of a recent paper by Gold.<sup>212</sup> He reviews his previous studies on digitoxin and calls attention to the rapid rate of absorption of the drug from the gastrointestinal tract and the rarity of toxic effects from the administration of a single oral digitalizing dose. He also emphasizes the occasional value of daily mercurial injections to control edema when other measures have failed.

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209. Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, *Am. Heart J.* **33**:14, 1947.

210. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiogram Obtained by Heart Catheterization in Man, *Am. Heart J.* **33**:604, 1947.

211. Chavez, I.; Dorbecker, N., and Celis, A.: Direct Intracardiac Angiocardigraphy—Its Diagnostic Value, *Am. Heart J.* **33**:560, 1947.

212. Gold, H.: Pharmacologic Basis of Cardiac Therapy (Alpha Kappa Lecture, Abridged), *J. A. M. A.* **132**:547 (Nov. 9) 1946.

Erickson and Fahr<sup>213</sup> have investigated some of the effects of lanatoside C in 39 patients with organic heart disease but without evidence of heart failure and in 14 normal controls. The drug was given by mouth, and the mechanical efficiency of the heart was subsequently estimated. These authors concluded that 87 per cent of their patients with organic heart disease showed an improved mechanical efficiency after digitalization whereas the 14 normal controls had a definite decrease in cardiac efficiency. It was their belief that digitalis exerts its action "primarily on the cardiac muscle by changing the mechanical efficiency of the heart" and that in the normal heart the drug acts as a poison.

Another view of the mode of action of the drug digoxin has been presented by McMichael and Sharpey-Schafer.<sup>214</sup> These English authors administered the drug intravenously and noted a lowering of both the right auricular pressure and the cardiac output in normal persons and in patients with anemia and cor pulmonale as contrasted with an increase in cardiac output in most cases of congestive failure. They believe that simple mechanical lowering of the right auricular pressure produces a similar effect and suggest that the major benefit derived from the drug may be a peripheral action on the veins, with consequent lowering of the venous pressure. In contrast to orthodox concepts, they draw attention away from the stimulating effect of the digitalis group of drugs on the myocardium itself. These writers have likewise found that simple control of rate in cases of auricular fibrillation does not produce any immediate change in cardiac output which cannot be accounted for by the accompanying fall in venous pressure. It is their suggestion that digoxin may accordingly be actually harmful when administered in cases in which high output heart failure exists, as, for example, in cor pulmonale, Paget's disease and anemia. This interesting new theory, while it may be applicable to the digitalis glycoside which McMichael and Sharpey-Schafer have studied, does not necessarily hold true for the entire group of digitalis preparations.

In an attempt to investigate further the clinical value of lanatoside C, Ray and LaDue<sup>215</sup> administered digitalizing doses of the drug intravenously to 62 patients with recurrent congestive heart failure who had been receiving a maintenance intake of digitalis leaf. Although

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213. Erickson, E. W., and Fahr, G. E.: The Effect of Lanatoside C upon the Physiologic State of Organically Diseased Hearts Before Symptoms and Signs of Heart Failure Appear, *Am. Heart J.* **29**:348, 1945.

214. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Intravenous Digoxin in Man, *Quart. J. Med.* **13**:123, 1944.

215. Ray, T., and LaDue, J. S.: The Intravenous Administration of Lanatoside C to Patients Taking Maintenance Doses of Folia Digitalis up to the Date of Hospitalization with Recurrent Congestive Heart Failure, *Am. Heart J.* **30**: 335, 1945.

it might have been expected that symptoms of digitalis intoxication would develop in many patients in this group, these authors report that only one such reaction occurred. Furthermore, it appeared that in 46 of the 62 cases definite clinical improvement was demonstrated. Such a study does not eliminate the necessity for caution in the administration of digitalis glycosides to patients who are known to have been receiving the drug.

The relationship of digitalis to the clotting mechanism has been the subject of a report by de Takats, Trump and Gilbert.<sup>216</sup> They observed 4 patients who experienced thrombotic phenomena possibly related to the use of digitalis, and, stimulated by these findings, they thereupon gave digitalis to 5 patients and determined their tolerance to heparin daily. They concluded that resistance to heparin developed as a result of digitalization and disappeared after the use of digitalis was stopped, and they reasoned that "digitalis favors the tendency to thrombosis." Employing the Lee-White method of determination of clotting time, Massie and his associates<sup>217</sup> also demonstrated a reduction in the clotting time in 24 patients who were receiving digitalis. These investigations may be related to the findings of Askey and Neurath,<sup>218</sup> who believe that because of the high incidence of fatal systemic embolism the administration of digitalis alone for congestive heart failure associated with auricular fibrillation and myocardial infarction is contraindicated. Such conclusions require further clinical study, however, as it is obvious that many of the patients who received digitalis were poor risks,

A study of changes in the plasma volume and in the body weight of normal subjects who were placed on regimens designed to promote diuresis has been described by Lyons, Jacobson and Avery.<sup>219</sup> Their results indicate that a reduction both in plasma volume and in body weight, with accompanying diuresis, will occur in normal persons who are placed on a moderately low salt diet with 9.0 Gm. of ammonium

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216. de Takats, G.; Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, *J. A. M. A.* **125**:840 (July 22) 1944.

217. Massie, E.; Stillerman, H. S.; Wright, C. S., and Minnich, V.: Effect of Administration of Digitalis on Coagulability of Human Blood, *Arch. Int. Med.* **74**: 172 (Sept.) 1944.

218. Askey, J. M., and Neurath, O.: Is Digitalis Indicated in Myocardial Infarction? *J. A. M. A.* **128**:1016 (Aug. 4) 1945.

219. Lyons, R. H.; Jacobson, S. D., and Avery, N. L.: The Effect on the Plasma Volume of Dehydration Produced by a Low-Salt Diet and Ammonium Chloride, *Am. Heart J.* **27**:353, 1944. Lyons, R. H.; Avery, N. L., and Jacobson, S. D.: Effect of Dehydration, Produced by Mercupurin, on the Plasma Volume of Normal Persons, *ibid.* **28**:247, 1944. Lyons, R. H.; Jacobson, S. D., and Avery, N. L.: The Change in Plasma Volume and Body Weight in Normal Subjects After a Low Salt Diet, Ammonium Chloride, and Mercupurin, *Am. J. M. Sc.* **211**:460, 1946.

chloride a day or who are given this diet plus "mercupurin" (mercurio-phylline injection) intravenously or who receive "mercupurin" alone. They point out that a diagnosis of subclinical edema is not justified merely because diuresis and loss of weight occur with the use of these measures.

Modell<sup>220</sup> has compared the value of 1.0 and 2.0 cc. doses of "mercupurin" in ambulatory patients with congestive heart failure. Using loss of weight as the measure of diuresis in 37 patients, he found that two injections of 1.0 cc. semiweekly were of greater benefit than was one injection of 2.0 cc. per week and that the addition of ammonium chloride increased the amount of weight lost by about 15 per cent with both methods. He also concluded that there was no essential difference between the diuretic effect of intramuscular injection of "mercupurin" and that of intravenous injection.

The use of "mercupurin" orally has received a limited clinical evaluation by Batterman and his associates.<sup>221</sup> These workers have given "mercupurin" in tablet form to 81 patients in varying doses and for time intervals up to forty-nine weeks, and they have reported effective diuresis in approximately 75 per cent of their cases. Toxic reactions included albuminuria, gastrointestinal symptoms, gingivitis and elevation of the blood nonprotein nitrogen level. Although the authors consider this method of clinical value, it should be stressed that the incidence of toxicity is high in comparison with that found with administration by intramuscular and intravenous routes and also that the oral route is ordinarily of no value when the parenteral route fails. Batterman and his associates advised rest periods between courses of the drug when it is given orally.

Reports of fatalities resulting from the intravenous injection of mercurial diuretics continue to appear from time to time, although it is obvious that such disasters are rare in view of the widespread use of these preparations. Wexler and Ellis<sup>222</sup> have described 2 such deaths and have called attention to the fact that no sudden deaths have been reported after the intramuscular administration of a mercurial drug. Three similar fatalities have been discussed by Volini, Levitt and

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220. Modell, W.: The Optimal Dose of Mercurial Diuretics, *Ann. Int. Med.* **20**:265, 1944.

221. Batterman, R. C.; DeGraff, A. C., and McCormack, J. E.: The Effectiveness and Safety of Mercupurin Administered Orally in Treatment of Congestive Heart Failure, *J. A. M. A.* **124**:1243 (April 29) 1944. Batterman, R. C.; DeGraff, A. C., and Shorr, H. M.: Further Observations on the Use of Mercupurin Administered Orally, *Am. Heart J.* **31**:431, 1946.

222. Wexler, J., and Ellis, L. B.: Toxic Reactions After Intravenous Injection of Mercurial Diuretics, *Am. Heart J.* **27**:86, 1944.

Martin,<sup>223</sup> who have published electrocardiograms taken soon after the injection in 2 of the cases, in both of which ventricular fibrillation was present. Waife and Pratt<sup>224</sup> have published the findings at autopsy on a 35 year old woman who died in uremia after receiving twenty-five mercurial injections intravenously and intramuscularly over the course of six months. Postmortem examination showed the presence of mercury nephrosis, with hemorrhagic areas in the liver, ileum and colon.

In an attempt to reduce the toxicity of mercurial preparations, Chapman and Shaffer<sup>225</sup> injected mercurial preparations intravenously into dogs at two or at five minute intervals; the injections were preceded by or at times accompanied with injection of ascorbic acid. Their results indicate that the lethal dose of meralluride ("mercuhydrin") for dogs was greater than the lethal dose of mercurophylline or mersalyl and theophylline. Death from the last two preparations resulted from ventricular fibrillation whereas death due to meralluride was associated with ventricular asystole. Their statistics suggest that the use of ascorbic acid prior to the injection of meralluride increases the size of the lethal dose and thus increases the margin of safety, a similar effect being obtained when ascorbic acid and meralluride are injected together. Less conclusive results were obtained when these experiments were repeated with the other two preparations. It has been suggested by Pines and his associates<sup>226</sup> that magnesium sulfate might also be of value in reducing the toxicity of mercurial preparations by protecting against ventricular fibrillation.

Griffith<sup>227</sup> has reported on the clinical use of "paredrine hydrobromide" (*p*-hydroxy- $\alpha$ -methylphenylethylamine hydrobromide), a drug which has several actions, including a pressor effect, slowing of the heart due to a vagus reflex and ventricular stimulation (perhaps by a lessening of the refractory period of cardiac muscle and by stimulation of the conducting tissues). He has employed this drug in heart block to

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223. Volini, I. F.; Levitt, R. O., and Martin, R.: Studies on Mercurial Diuresis: V. Sudden Death Following Intravenous Injection; Report of Three Cases with Electrocardiographic Studies in Two, *J. A. M. A.* **128**:12 (May 5) 1945.

224. Waife, S. O., and Pratt, P. T.: Fatal Mercurial Poisoning, Following the Prolonged Administration of Mercurophylline, *Arch. Int. Med.* **78**:42 (July) 1946.

225. Chapman, D. W., and Shaffer, C. F.: Mercurial Diuretics: A Comparison of Acute Cardiac Toxicity in Animals and the Effect of Ascorbic Acid on Detoxification in Their Intravenous Administration, *Arch. Int. Med.* **79**:449 (April) 1947.

226. Pines, I.; Sanabria, A., and Arriens, R. T. H.: Mercurial Diuretics: The Addition of Magnesium Sulphate to Prevent the Toxic Effects of Their Intravenous Administration, *Brit. Heart J.* **6**:197, 1944.

227. Griffith, G. C.: Use of Paredrine Hydrobromide, *U. S. Nav. M. Bull.* **44**:284, 1945.

prevent Adams-Stokes attacks as well as in auricular and ventricular tachycardia and in auricular fibrillation and has had encouraging results. Although the physiologic and pharmacologic effects of the preparation appear to be somewhat contradictory, a further investigation of its uses is anticipated.

In conclusion, a few words are appropriate to emphasize the recent major advances in the study of cardiovascular problems. Knowledge of cardiac function in health and in disease is steadily increasing as a result of the use of new biochemical methods and the introduction of new investigative technics, notably cardiac catheterization. In particular, many cases of congenital heart disease can thus receive more adequate diagnostic study, which leads often to surgical intervention, with resultant cure or with significant clinical improvement. Dietary management of heart failure has now been recognized as of established value, and the dietary control of hypertension holds interest for the future. The availability of unlimited quantities of penicillin and streptomycin has permitted a profound drop in the mortality of bacterial endocarditis. Finally, special foundations, governmental agencies and the public at large have acquired a greater realization of the need for intensive research in the field of cardiovascular diseases and are now making possible investigative projects which may further broaden our knowledge.



## News and Comment

### GENERAL NEWS

**Resolution on Nurse Anesthetists.**—At the meeting of the Southern Surgical Association which was held in Hollywood, Florida, Dec. 9, 10 and 11, 1947, the following resolution was passed unanimously by the Association:

"Although the Southern Surgical Association has been and always will be extremely interested in the advancement of all medical sciences and particularly in anesthesia, because of complete dependence on safe anesthesia for the safe performance of a surgical procedure, it, the Southern Surgical Association, heartily disapproves of the publicity given by certain newspapers and popular lay magazines to the statement sponsored by a group of anesthesiologists who are seeking to discredit the well trained nurse anesthetist and to compel surgeons to operate only if anesthetics are administered by physician-anesthetists.

"This attempt to persuade the public that there is grave danger in a surgical operation if the anesthetist is not a certified medical specialist is already decreasing the number of efficient well trained nurse anesthetists and forcing surgeons to perform recently developed complicated operations with anesthetics administered by young hospital interns or general practitioners, neither of whom have special training or experience in the administration of an anesthetic."

**Biological Photographic Association.**—The Biological Photographic Association will hold a meeting at Houston Hall, University of Pennsylvania, Philadelphia, from September 8 to 10. There is to be an interesting exhibit of prints, color transparencies and motion pictures in the field of biologic photography. Organized symposiums and demonstrations are planned.

Further information about the meeting and about the Biological Photographic Association may be secured by writing to the secretary at University Office, Magee Hospital, Pittsburgh 13, Pa.

**1949 Annual Session of the American College of Physicians.**—The American College of Physicians will conduct its thirtieth annual session in New York City from March 28 through April 1, 1949. Dr. Franklin M. Hanger Jr., of New York City, is the chairman for local arrangements and for the program of clinics and panel discussions. The president of the college, Dr. Walter W. Palmer, Director of the Public Health Research Institute of the City of New York, Inc., and Professor Emeritus, Columbia University College of Physicians and Surgeons, is in charge of the program of morning lectures and afternoon general sessions.

Secretaries of medical societies are especially asked to note these dates and, in arranging meetings for their societies, to avoid conflicts with the college meeting for obvious mutual benefits.

**Orientation Course in Allergy.**—Northwestern University Medical School, Chicago, and the American Academy of Allergy are offering an orientation course in allergy to be given during the week of Oct. 25 to 29, 1948, inclusive. The faculty includes many men of national prominence.

## Book Reviews

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**Mental Mischief and Emotional Conflicts.** By William S. Sadler, M.D.  
Price, \$6. Pp. 396. St. Louis: The C. V. Mosby Company, 1947.

Whenever a writer attempts to explain so complex a subject as the human personality, with its conflicts and its disharmonies, in a style suited to the lay reader, all too often the result is oversimplification. In thirty-four chapters Dr. Sadler discusses practically all problems which a busy psychiatrist is likely to encounter in any single month of practice. After a few chapters devoted to basic concepts of psychopathology, he separately discusses the various neuroses, character disorders and nonorganic psychoses and concludes with a chapter devoted to psychotherapy and one on "A Philosophy of Life."

The subtitle of this pretentious work is "Psychiatry and Psychology in Plain English." In spite of this warning, the reviewer was surprised to see the problem of multiple personality traits presented as manifestations of the "personality gear shift." Another cliché likely to catch the eye of the reader is "psychic indigestion." The problem of fatigue in psychasthenia is said to lie in the fact that "psychasthenes are born tired and remain so most of their lives." The reviewer was also surprised to learn that neurasthenia, while worldwide in distribution, is more prevalent in the Rocky Mountain region, "probably because of the extra strain imposed upon otherwise predisposed nerves by the dry climate, stimulating altitudes, strong winds and excessive sunshine." Were this advice to be taken seriously, I suppose that we of the central, southern and eastern states should hasten to dissuade many from the vacations contemplated in the approaching months.

Religious and occult thought is to some writers useful in explaining phenomena which baffle the scientific mind. A paragraph in the explanation of neurotic symptoms found under the heading of "Occult Deceptions" tells us that "Neurotics do actually experience the sensations and suffer the agonies which they so pathetically tell their doctor. Although they are tricked by their imaginations they are not intentionally dishonest—they are unfortunate victims of their unconscious mind." This explanation is plausible, but many will object to the comparison of the neurotic patient with the honest psychopath. "The honest psychics," says the author, "really believe they possess psychic powers just as truly as neurotics believe in the reality of their ailments."

To say the least, the explanation of telepathic phenomena is unusual. Dr. Sadler leads us to "suspect that there exists a universal spiritual intelligence—a universal mind." He then asks: "Is it too much to suspect that there may be a Universal Intelligence whose emanations radiate to everyone who is in harmony with the Divine Mind?" He concludes that "it is not hard to understand that two minds might think the same thing at the same time, just as two radio stations may receive at the same instant a message from a vessel far out at sea." The reviewer must unfortunately admit that to hold such an opinion is indeed difficult.

Dr. Sadler concludes his book with an observation that religions of modern times have been in danger of growing weak and effeminate, that what is needed is more of the spirit of the carpenter's Son and that faith and determination in the pursuit of the higher and nobler aims of life are necessary. But since persons with psychasthenia and neurasthenia, paranoia and schizophrenia, neurosis and psychosis

make up a sizable proportion of the earth's population, the reviewer is at a loss to know how the step from worldly to Christlike teachings can be accomplished. Dr. Sadler does not elaborate on this point.

The book has an adequate index and a representative bibliography.

**Penicillin in Syphilis.** By J. Earle Moore, M.D. Price, \$5. Pp. 332, with 57 illustrations. Springfield, Ill.: Charles C Thomas, 1947.

Dr. Moore was one of the first in this country to develop a clinic in which syphilis was dealt with as a branch of general medicine and to correlate his work with those ancillary laboratories for experimental study which are so effective in promoting sound practice in their vicinity. As his long and extensive clinical experience developed, it was inevitable that a book should appear from his pen and "Modern Treatment of Syphilis," previously reviewed in these columns, has been everywhere recognized as a landmark in the literature of the disease. During the war, through the Subcommittee on Venereal Disease of the National Research Council, Moore was one of the leaders in correlating civilian and military efforts to control and treat syphilis, and finally, as chairman of the Penicillin Study Panel, he has woven together the threads of knowledge which converge from clinics over the country in which the new antibiotics have been tested under his supervision. No one is better fitted, therefore, to bring out the first monograph on penicillin in syphilis, and the reader will not be disappointed. The subject is gone into with great thoroughness, beginning with sections on chemistry, pharmacology, toxicity and the action of penicillin in experimental syphilis and a discussion on the mechanism of action of penicillin. Early, latent and other types of syphilis are then taken up in detail. The whole thing is a living story of what has already been accomplished and what is now being done, with emphasis throughout on the limitations of the data so far available, the necessarily tentative character of the conclusions and the inevitability of changes, in the future, in present programs of treatment.

The book is written in Dr. Moore's simple and lucid but entertaining style. There are numerous tables, charts and illustrations. The literature is fully reviewed. In short, this monograph is definitive to date and must be the basis of departure for all future studies on the subject.

**Gynecology, with a Section on Female Urology.** By Lawrence R. Wharton, M.D. Second edition. Price, \$10. Pp. 1,027, with 479 illustrations. Philadelphia and London: W. B. Saunders Company, 1947.

The second edition of this combined textbook has been brought up to date in the ever changing fields of endocrinology and therapeutics. Recent advances in both fields as applied to women are well outlined. The advances made in the detection and treatment of genital cancer are current and thoroughly discussed.

In general, as a textbook for students in the field of gynecology, the author has arranged and presented his subject matter in a clear and, for a textbook, enjoyable fashion, with documentation of disputed points and an undogmatic attitude. The section on menstruation and related phenomena is especially clear and understandable from a student's point of view. Operative gynecology has not been emphasized at the expense of office treatment, but the procedures advocated have been clearly stated both in the text and pictorially. The section on female urology emphasizes the close relationship of the latter to gynecology, a fact too often overlooked. Certainly, the gynecologist must be familiar with urologic principles in dealing with many conditions in which the specialties overlap.

In a few instances omissions are noted. For instance, in the treatment of functional uterine bleeding, the use of the male hormone is encouraged, whereas control of the condition with progesterone or with combined estrogen and progesterone therapy is mentioned in passing. The latter is more physiologic and certainly more widely used. Again, the book makes little or no mention of the adrenal hormones as related to gynecology. When discussing subtotal hysterectomy versus total hysterectomy, the author advocates the widespread use of the former, in contrast to the growing tendency in favor of the latter. Although it is true that cases should be individualized and that more skill is required for the total procedure, the reviewer believes that it should be encouraged as a means of prophylaxis against cervical carcinoma.

In spite of a few differences of opinion, this second edition is a welcome addition to the literature and should be especially useful to undergraduate students.

**Principles and Practice of Medicine.** By Henry A. Christian, M.D. Sixteenth edition. Price, \$10. New York: D. Appleton-Century Company, Inc., 1947.

Although the familiar format is maintained, one notes that Osler's name no longer appears on the back strip of this sixteenth edition of the famous textbook. The Osler tradition is, however, preserved in an essay by Dr. James G. Carr dealing with the progressive changes in the book from the first edition in 1892 through those compiled by McCrae and by Christian up to the present time.

No one could be better fitted to take over the important burden of preparing a textbook than Dr. Christian. He has thoroughly revised and brought up to date all the material in a precise and scholarly way. Space forbids detailed analysis. It may be said, however, that the general method of arrangement and classification used in recent editions is continued. Some of Osler's original descriptions still remain and indeed cannot be surpassed, although such phrases as "among women, anemic, dyspeptic servant girls seem very prone (to peptic ulcer)" are perhaps a bit archaic in this day when servants no longer exist. There is always the question of allocation of space to various subjects. The reviewer still maintains, as he did in regard to a former edition, that thirty pages need no longer be devoted to typhoid fever nowadays when the disease is rarely seen, and that some of this space could be used to discuss other infections such as virus diseases, which are all dealt with in about seventy-five pages, of which only fourteen are assigned to the important group of encephalitides including poliomyelitis. On the other hand, there is practically nothing in the domain of internal medicine which is not at least touched on, and the book remains invaluable for student, physician and teacher.

**Leprosy.** By Sir Leonard Rogers and Ernest Muir. Third edition. Price, \$7. Pp. 280. Baltimore: Williams & Wilkins Company, 1946.

In this book a three thousand year old subject is effectively handled by two competent authors who have had extensive experience with the material in the Orient and elsewhere. The book proper is divided into six sections: history and distribution, epidemiology and communicability, prophylaxis, etiology, clinical observations and treatment. These sections are followed by appendixes containing eighty-eight photographs. The material is well organized, with an index and bibliography.

The history of the disease is recognized as being inseparable from the clinical aspect and is infiltrated throughout the book, forming the background on which our sparse scientific knowledge of this disease is presented. Along with the history is the presentation of the public health attitudes, both ancient and modern.

The section on treatment is up-to-date (including a consideration of calcium, penicillin and streptomycin). The current drugs are considered concisely and in the light of the authors' extensive experience.

The book is readable and does not bog down with details. It gives a comprehensive and clear picture, leaving minutiae for the research worker to supply in other books.

**Tumores y pseudotumores de la mama.** By Dr. Jacinto Moreno. Price, \$8.

Pp. 142. Buenos Aires: Lopez & Etchegoyen, S. R. L., 1946.

This book is a study on the experimental investigation of mammary tumors, in which special consideration is given to their objective anatomic pathology and clinical diagnosis. The author starts his discussion with a classification of the mammary tumors. Each pathologic entity is individually presented, and representative photomicrographs, with excellent descriptions, are included in the discussions. Emphasis is given to the management and endocrine therapy of functional mastopathy.

The treatment of mammary cancer is extensively discussed by the author. He presents a statistical review, trying to estimate his skepticism on the surgical treatment of mammary neoplasms, in which it appears that the unsatisfactory results from this form of treatment are too strongly emphasized.

A discussion is included on the prophylactic treatment of carcinoma of the breast, based on the restoration of hormonal balance with the use of thyroid, insulin and ovarian extracts according to the author's experience.

**Intracranial Complications of Ear, Nose and Throat Infections.** By

Hans Brunner, M.D. Price, \$6.75. Pp. 444. Chicago: Year Book Publishers, Inc., 1946.

Brunner has assembled his experiences with intracranial infections encountered in otorhinologic practice in Vienna and Chicago during the last quarter century. The monograph is written for the otorhinologist and neurologist and will be of primary interest to the former. The major intracranial complications of infections of the ear, nose and throat are thoroughly discussed, with emphasis on genesis, symptomatology and treatment. The book appears to have been hastily composed. Many chapters lack coherence, unity and clarity but not verbosity. Grammatical errors frequently distract the reader's interest and attention. Dr. Brunner is an eminent authority in otolaryngology, and the book contains a wealth of valuable material; nevertheless, the presentation is impaired by a deficiency in correct English grammar.

**Techniques and Procedures of Anesthesia.** By John Adriani, M.D. Price, \$6.

Pp. 418. Springfield, Ill.: Charles C Thomas, 1947.

This text is written in tabular fashion, which makes it an excellent ready reference for the busy practitioner who occasionally has to administer an anesthetic. This style of presentation makes the contents rather too rigid and with too much emphasis on trivia for use by students. Specialists in anesthesiology will object to many dogmatic statements, which would undoubtedly have been qualified were the book written in ordinary running prose form.

An introductory chapter on the nature of anesthesia and its manifestations could well have been included. This could have been in the usual literary style to good advantage. As the book now stands, the emphasis is on technics rather than on the more important physiologic considerations.

**Fundamentals of Clinical Neurology.** By H. Houston Merritt, M.D.; Fred A. Putnam, M.D., Ph.D., and Tracy Jackson Putnam, M.D. Price, \$6. Pp. 289, with 96 illustrations. Philadelphia: The Blakiston Company, 1947.

This excellent book represents an effort to give a thorough discussion of neurologic diagnoses without entering the domain of controversial or esoteric neuroanatomy or physiology. While it follows in general plans which have previously been used by others, there are a number of outstanding features: fine paper and good type, numerous reproductions of anatomic preparations, lucid diagrams of nervous pathways and centers, practical clinical diagnostic tables and photographs of patients with various clinical lesions. The reviewer believes that this book fulfills very well the authors' purpose of aiding the general physician in the fundamentals of clinical neurology.

**Clinical Hematology.** By Maxwell M. Wintrobe, M.D., Ph.D. Second edition. Price, \$11. Pp. 862, with 197 illustrations and 14 plates, 10 in color. Philadelphia: Lea & Febiger, 1946.

This revision of Dr. Wintrobe's excellent treatise brings the subject of hematology fully up to date. However, the greatest feature of the book is its really comprehensive handling of the subject. The introductory chapters on the blood and the blood cells are obviously from the pen of an authority who has done original work in the field. The discussions of disease are satisfying and deal in a critical way with the many intriguing problems of pathogenesis. There are innumerable excellent drawings and charts, and each chapter is followed by a really full bibliography. It is a comparable work from the standpoint of thoroughness and scholarship.

**Pharmakologie als theoretische Grundlage einer rationellen Pharmakotherapie.** By K. O. Moller. Price, 48 Swiss francs. Basel: Benno Schwabe & Co., 1947.

It is stimulating to find such an extremely satisfactory book coming out of war-torn Europe. The author is obviously an accomplished scholar and thoroughly familiar with his subject in an authoritative way. His idea has been to bridge the gap between pharmacology and clinical medicine. To effect this end, he discusses first the chemistry and pharmacology of various substances and then describes the clinical applications. Innumerable preparations are taken up, so that the book really becomes a small encyclopedia. The information given is up up-to-date and in line with sound practice. The book is well printed on good paper and is not paralleled by any English work as far as is known. It is to be highly recommended.

**Diagnostic electrocardiographique.** By André Jouve, Jacques Senez and Jean Pierron. Price, 860 francs. Pp. 364, with 217 illustrations. Paris: Masson & Cie, 1946.

This monograph is essentially of the usual type. The material is presented without too much attention to the mechanisms for the various electrocardiographic complexes encountered in normal and diseased states. The illustrations are fairly good. Some of the more recent publications on electrocardiography have not been included, an omission most probably due to the war. This monograph is not to be particularly recommended except as a source of information for those who are curious about the manner in which electrocardiography is practiced and taught in France.

Annual Review of Physiology. Volume IX. Price, \$6. Pp. 736. Stanford University, Calif.: Annual Reviews, Inc., 1947.

The ARCHIVES saluted this important book shortly after the first volume had appeared. Subsequently, the second, third and fourth volumes were received with the same enthusiasm that greeted the first.

The ninth volume is like its predecessors and lives up to their standards. The "Annual Review of Physiology" is intelligently compiled; it is written by a carefully selected list of contributors and each chapter concludes with an admirable list of bibliographic references. Each supplement continues to make the series an indispensable tool for those interested in internal medicine and its advances.

The Compleat Pediatrician. By Wilburt C. Davison, M.D. Fifth edition. Price, \$4. Durham, N. C.: Duke University Press, 1946.

Revised and rewritten to include newer advances in pediatrics, the fifth edition of this book presents a concise, up-to-date digest, combining in one volume the practical pediatric facts usually found in several. Used for the purpose intended, it should be of invaluable aid to any physician who deals with infants and children. It is recommended most highly to student and practitioner alike.

Principles and Practice of Tropical Medicine. By L. Everard Napier. Price, \$11. Pp. 917. New York: The Macmillan Company, 1946.

The events of World War II brought tropical medicine into sharp focus and stimulated the appearance of numerous articles and several books on the subject. The author of this volume, like previous authors, also has had difficulty in deciding what diseases to include under the title of "tropical diseases." Thus one observes the omission of the most prevalent one, tuberculosis, and others of importance, such as typhoid and tetanus, but finds the inclusion of tularemia, which the author states is caused by *Brucella* (sic!) *tularensis*, seven day fever of Japan, Rocky Mountain spotted fever, Weil's disease, trichinosis and the tapeworm infection due to *Diphyllobothrium latum*—all nontropical diseases.

There are a number of misleading statements, such as the statement that undulant fever occurs in the southern states of the United States of America, with no reference to its greater frequency in the North Central States, and, with reference to coccidiosis, that a heavy infection "will cause a catarrhal condition of the mucosa rather than ulceration and will interfere with its (small intestine?) functions." The statement that Iceland is an important focus of hydatid disease has not been true for forty years, and this should be known generally.

The author evidently has had little access to the literature on the results of observations made during the war. For example, most of the recent work concerning typhus and its dramatic control in Italy and elsewhere is not referred to, nor is there any reference to the work done by the United States Army and Navy with reference to filariasis. It is in the section dealing with malaria that the most obvious omissions and lack of recent information are revealed. Some of the most obvious errors may be indicated as follows: 1. Pamaquine naphthoate is said to enhance the action of quinine and quinacrine hydrochloride in completely eradicating a benign tertian infection and thereby preventing a relapse. 2. The dose of quinacrine hydrochloride is given as 0.1 Gm. three times a day for five days, with no reference to the demonstration that such a dose is inadequate to control attacks of malaria. 3. In a discussion of the complications in administration of quinacrine hydrochloride, no reference is made to lichen-planus-like cutaneous lesions, which

have been thoroughly studied. 4. Pyrethrum is given as the repellent of choice in India before the introduction of DDT (4,4'-dichlorodiphenyltrichloroethane), neither one of which is generally considered to be a repellent, however. The author gives oil of citronella a prominent place as a repellent and in a three line note refers to dimethylphthalate, "indalone" (butyl ester of 3,4-dihydro-2,2-dimethyl-4-oxo-1,2-pyran-6-carboxylic acid) and "612 insect repellent" (2-ethyl-1,3-hexanediol). He recommends their use in a shellac paint, a method attempted in experiments but not successful. There is, however, no discussion of these important repellents. A discussion of DDT is limited to a line or two in the following phraseology: "It seems possible that DDT eventually will replace Pyrethrum as the insecticide." These are but a few of the examples which could be cited of instances in which the author has failed to record well known recent observations which have served to advance knowledge of tropical medicine.

The author does not dwell on laboratory methods of procedure; however, he does give numerous procedures throughout the text. There are a number of prominent omissions, however, in these procedures, an example of which is the importance of the acid-ether concentration method for the detection of the ova of *Schistosoma* and other worms. There is no discussion of the poisonous plants of the tropics, but there is a section dealing with snakes. There are a number of illustrations in the text, many of which have been drawn from articles by other authors, but for the most part reproduction of the figures has not approached the quality of those in other texts on the subject.

In spite of these criticisms, the book does contain a considerable amount of useful information, especially that which has been gained by the author's personal experience, and if read with discretion it may prove to be of use to the clinician whose access to other texts may be difficult.

**Fosforyleringsprocessers betydning for resorption og assimilation.** By Kaj Kjerulf-Jensen. Pp. 191. Copenhagen: Arnold Busck, Nyt Nordisk Forlag, 1942.

This monograph, published in August 1942, but reaching the United States just recently, describes further studies, undoubtedly inspired by Professor Lunsgaard, which continue the brilliant work on absorption coming from the Copenhagen laboratories. As the author states, "the main purpose of the present investigations has been to demonstrate the significance of phosphorylation processes for the mechanism of active absorption of monosaccharides and amino acids and for the assimilation of monosaccharides."

The book is divided into two parts. Part I, consisting of eight chapters, reviews current opinion on the absorption of specific monosaccharides from the intestinal tract and discusses the role of various phosphorylating systems (donors and acceptors), glycogen formation, absorption by the renal tubule and the chemical nature of phosphorylated compounds participating in these reactions. The section closes with a brief discussion of the possible hormonal regulation of these processes and observations on the simultaneous absorption of glucose with galactose, glycin or fatty acid, causing a reduction in the absorption rate of glucose, which the author thinks may indicate a common absorption mechanism of these substances.

Part II, also of eight chapters, describes methods and experiments and presents data obtained. Observations are made on the pronounced decrease in inorganic phosphate, accompanied with a moderate increase in acid labile phosphate, probably adenosintriphosphate, in the intestinal mucosa during the absorption of amino acids such as glycine, alanine and glutamic acid. Phosphorylation of adenylic acid in



the intestinal mucosa "probably only takes place because amino acids are unsuitable as phosphate acceptors." The author expressed the opinion that present evidence does not justify the assumption of an intermediary phosphorylation of amino acids during absorption. He demonstrated the accumulation of fructose-1-phosphoric acid in the intestinal mucosa of rats during the absorption of fructose. Inhibition of absorption of glucose and galactose by phlorhizin poisoning (which interferes with phosphorylation) was confirmed. On the other hand, the rate of absorption of fructose was uninfluenced by phlorhizin in the rabbit and decreased about 10 per cent in the rat. The author's experiments confirmed previous observations of Robinson and Tanko that fructose-1-phosphoric acid cannot be dephosphorylated selectively, i. e., transformed into the corresponding glucosephosphoric acid, which probably accounts for the accumulations of fructose-1-phosphate within the mucosa during fructose absorption. In the final chapter, evidence is produced by the use of radioactive phosphorus to show that in the rabbit about 15 mg. of fructose can be absorbed from the intestine per minute. It forms fructose-1-phosphoric acid in the intestinal mucosa and is rapidly renewed.

The monograph has an excellent summary in English. It is also stated that a description in English of the experimental work may be found in *Acta Physiologica Scandinavica*, 1942.

**Science and Scientists in the Netherlands Indies.** Edited by Pieter Honig and Frans Verdoorn. A Review of Research and Exploration in the Netherlands Indies. Prepared Under the Auspices of the Board for the Netherlands Indies, Surinam and Curaçao. Price, \$4. New York: Board for the Netherlands Indies; G. E. Stechert, 1945.

This book is worth reading. It gives an attractive account of life in the Netherlands Indies as observed through the eyes of men with scientific training. One gets an idea not only of the country but also of the people, the climate, the plant and animal life and the history that has made civilization go forward there so steadily.

There are several chapters which deal with medicine. Donath and van Veen describe the fundamental researches on beri-beri by Eijkman, who proved that vitamin B<sub>1</sub> was the important factor in the disease. There are five sections which tell the story of cultivation of quinine. An article by Otten van Stockum outlines her researches on rabies—unfortunately interrupted by her death. De Waart discusses medical education in that part of the world, stating that a medical school was opened in Batavia in 1852 and showing how since then medical education in the Netherlands East Indies has progressed satisfactorily. Perhaps the most interesting part of the volume dealing with medicine is prepared by Snapper, who summarizes much of what has been done to improve public health. Vaccination for smallpox was introduced in 1804 by keeping the vaccine alive on the way from Mauritius to Batavia through a few healthy children who were vaccinated successively on the journey; now smallpox there has been practically eradicated. Malaria has been controlled. Cholera has been made to disappear. Plague is much less serious than it was thirty years ago. Snapper's concluding words seem well taken: "The physicians of the Netherlands owe a debt of gratitude to their colleagues who have transformed the notoriously unhealthy Netherlands Indies into a healthy territory."

One of the underlying purposes of the book is to find readers who will feel drawn to the Malaysian Islands and who will offer their scientific training and knowledge for the good of mankind in that region. It is a stimulating challenge to anyone with the blood of adventurers or pioneers in his veins.

**Adolescent Sterility.** By M. F. Ashley-Montagu. Price, \$3.50. Pp. 159. Springfield, Ill.: Charles C Thomas, 1946.

The author of this monograph has a gift for writing, so that he can make the commonplace unusual and any subject out of the ordinary of absorbing interest. His approach to any discussion is always the scholar's; his use of English is excellent, his way of thinking is logical and his conclusions are sharply pointed. For these reasons, if for no other, his publications are worth reading.

Many years ago he became curious about the basis for the well known anthropologic belief that women rarely produce children until several years after their onset of menstruation. Here he has assembled all the available information on this broad subject; it proves to include not only a considerable volume of experimental data but also a wealth of clinical observation.

His conclusions seem reasonable. He thinks that in the human species conception is possible at or even before the first estrus; when it occurs near the commencement of the first menstruation, however, there is generally a high infant and maternal death rate. The physical changes of puberty are normally followed, after the lapse of a variable amount of time, by ovulation. This takes place through a complicated interplay of anterior pituitary hormones, including the effect of one which acts on the ovary in such fashion as to cause an ovum to break through the ovary, to pass into the uterus and to luteinize, leaving behind its follicular investment.

In the uterus, under the influence of another anterior pituitary hormone, prolactin, the deposited ovum continues to undergo organization into a luteal body, and this secretes a hormone, progesterone, which prepares the uterus for pregnancy. It is not until prolactin is secreted and the corpus luteum produces progesterone that successful pregnancy becomes possible.

This monograph will interest clinicians who have dealings with endocrinology as well as experts in the field. It is a carefully thought out and ingeniously reasoned presentation.

**Physical Chemistry of Cells and Tissues.** By Rudolph Höber, with the collaboration of David I. Hitchcock and others. Price, \$9. Pp. 676, with 70 illustrations. Philadelphia: The Blakiston Company, 1945.

This is a "renaissance" rather than a revision of Höber's earlier book in German by the same title and consists of separate sections by various authors, covering certain aspects of physical chemistry and physiology. The title emphasizes the former because of the conviction of the authors that "it is not only possible but of importance to anchor physiology even deeper in physical chemistry than was done previously."

The subject matter is arranged systematically from the standpoint of complexity. The first two sections comprise a survey of classic physical chemistry—selected topics in physical chemistry by David I. Hitchcock and properties of large molecules by J. B. Bateman. The subsequent six sections deal with the physiology of cells and tissue—permeability of cells and properties of cell membranes by Rudolf Höber; influence of ions and narcotics on cell activity (Höber); respiration of cells and tissues by David R. Goddard; contractility of muscle by Wallace O. Fenn, and passive penetration and active transfer in animal and plant tissues (Höber). The topics discussed, too numerous to be listed here, include the formation of urine, gastric juice and saliva, intestinal absorption, respiratory enzymes and many others of interest to those engaged in medical research.

In general, the book is the embodiment of a point of view rather than a comprehensive treatise on physiology. It is of particular interest in providing a different approach than the majority of texts on the subject, in giving the physicochemical background of many of the concepts of physiology and in including data on a great variety of species. The individual sections are clearly organized and well written, and they provide excellent surveys for the scientifically trained general reader. For the material covered, the book is a valuable source of reference, with good author and subject indexes, almost two thousand references to the literature (through 1943) and general bibliographies in connection with each section.

**Estudio crítico del tratamiento médico de la insuficiencia cardíaca.** By Blas Moia, M.D. Pp. 107. Buenos Aires: El Ateneo, 1945.

This work has been written with the purpose of sharply defining the indications for and actions of the therapeutic recourses of undisputed value in the treatment of congestive heart failure. The study has been made bearing constantly in mind the modern concepts of cardiac pathologic physiology which by enlarging fundamentally the knowledge of the mechanism of heart failure have narrowed the limits to which the therapeutic scheme must be adjusted. Presented in conjunction with the author's basic material are abundant and extensive references to European and American investigators.

The monograph's introductory chapter logically consists of a comprehensive and explicit discussion on the pathologic physiology of congestive heart failure. Having presented these fundamentals, the author proceeds in the second chapter to discuss the use of digitalis compounds in cardiac insufficiency. The literature on the subject is thoroughly reviewed, and a critical study is presented, based on the author's own observations. The final chapter is an evaluation of therapeutic measures of common use in the treatment of cardiac failure, most of which are designed to diminish directly or indirectly blood stasis and its effects. In succession, the author discusses the problems of diet, choice and use of diuretics, indications for and technic of phlebotomy, laxatives, physical and mental rest, sedation, uses of hypertonic glucose solutions and oxygen therapy. These measures being of basic importance in the management of congestive failure, the author lays particular stress on their significance, emphasizing their consideration in the medical regimen of the pregnant patient with cardiac disease.

The physiologic approach considerably enhances the effectiveness of the presentation of this critical study. For the reader interested in a further exploration of the literature on the subject there is listed an extensive bibliography.

## TEMPORAL ARTERITIS

Review of the Literature and Report of Five Additional Cases

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**B**ENIGN arteritis and periarteritis of the temporal arteries was first described as a distinct clinical entity in 1932 by Horton, Magath, and Brown.<sup>1</sup> Since this time there have been reported in the literature 43 cases which seem to fall into the category of temporal arteritis. This disease is characterized by systemic symptoms of fever, anorexia, malaise, loss of weight and weakness; and local symptoms consisting of tender, swollen, nodular and thrombosed temporal arteries, with severe throbbing headache. Edema around the involved vessels is common. Pain in the adjacent structures, such as the scalp, face, jaws, eyes and temporo-mandibular joints, is also seen fairly constantly. Blindness has been a distressingly frequent complication of the disease. Some investigators, notably Cooke and his co-workers<sup>2</sup> and Chasnoff and Vorzimer,<sup>3</sup> have suggested that the disease is neither as benign nor as localized as was formerly thought. In order to evaluate this entity more accurately the essential data of all the reported cases were collected for critical analysis.

The fact that the disease is not as uncommon as the paucity of reported cases would indicate is suggested by the fact that Horton and Magath<sup>4</sup> were able to collect 7 cases by 1937 and Cooke and his associates<sup>2</sup> reported 7 cases seen in a four year period. Several other unreported cases are known to the authors.<sup>5</sup> Two cases here reported have been

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Read before the Bangor Medical Club, Jan. 24, 1947.

From the Departments of Medicine and Pathology, Tufts College Medical School, Post-Graduate Division.

1. Horton, B. T.; Magath, T. B., and Brown, G. E.: Proc. Staff Meet., Mayo Clin. 7:700-701 (Dec. 7) 1932; Arteritis of Temporal Vessels: Previously Undescribed Form, Arch. Int. Med. 53:400-409 (March) 1934.

2. Cooke, W. T.; Cloake, P. C. P.; Govan, A. D. T., and Colbeck, J. C.: Quart. J. Med. 15:47-76 (Jan.) 1946.

3. Chasnoff, J., and Vorzimer, J. J.: Ann. Int. Med. 20:327-333 (Feb.) 1944.

4. Horton, B. T., and Magath, T. B.: Proc. Staff Meet., Mayo Clin. 12:548-553 (Sept. 1) 1937.

5. (a) Heusner, A. P.: Personal communication to the authors. (b) Wilson, S.: Personal communication to the authors.

seen at the Eastern Maine General Hospital within a six month period. Three additional cases seen at the Joseph H. Pratt Diagnostic Hospital in Boston are briefly reported. All 5 cases fulfil the essential criteria of the disease entity. This brings the total of reported cases to 48.

#### REPORT OF CASES

CASE 1<sup>st</sup>.—*History*.—C. M., a 73 year old housewife, was admitted to the hospital on July 6, 1946 because of blindness in the left eye. She had been well, except for chronic arthritis of mixed type, until two months before admission, when a steady throbbing headache developed over both temples and across the forehead. This had been associated with "swelling and redness of the veins of the forehead." She had noticed also that these "veins" were nodular and pursued a tortuous course. The nodules had been particularly sore and tender. Redness and swelling were present, extending about 1 cm. to either side of the "veins" all along their course. The aching had also been behind the eyes, in the eyeballs and over the upper part of the face. Treatment for "sinus trouble" had not afforded relief. There had been no hemicrania, nausea, vomiting, rhinorrhea or postnasal discharge. There was no swelling of the face or stiffness of the temporomandibular joint.

One week before admission she noticed "black spots" before the eyes, especially on the left side. Two days before admission on awakening there seemed to be a "black cloud" before her left eye. This cleared up in about an hour. The day before admission on awakening there seemed to be the same cloud over the temporal aspect of the left visual field, which also subsided in about an hour. Throughout the remainder of each day her vision seemed normal. On the day of admission she was unable to see anything with the left eye.

During the week prior to admission the headache had become much less severe and persisted only as a dull nagging bitemporal ache. She had lost about 20 pounds (9 Kg.) in weight during the present illness. She also knew that she had been having a low grade fever with a temperature up to "around 100 degrees" during this illness. Her appetite was poor.

The past history and review of systems were noncontributory. The mother and a brother had died many years previously of tuberculosis.

*Examination*.—Examination showed some evidence of recent loss of weight. The temporal arteries showed marked tortuosity, slight swelling and moderate nodularity. They were slightly tender to touch, and the nodules were especially tender. Compression of the arteries at their origin seemed to relieve the headache. There was no edema or redness of the skin at this time, but it was somewhat indurated. There was no tenderness of the mastoids or sinuses. The pupils were unequal, the left pupil measuring approximately 4 mm. in diameter and the right pupil 3 mm. Only the right pupil reacted to light and both reacted in accommodation. The ophthalmoscopic examination of the left eye revealed that the media were clear; the retina appeared grossly normal and the nerve head, which was faintly yellow, was fairly well outlined, especially in the temporal half, but without physiologic cupping. The arteries were narrow and tortuous, with a widened central light band. The size proportion of arteries to veins was approximately 1 to 3. The veins were somewhat full, and quite tortuous and showed segmentation in some areas, giving the appearance of broken columns of blood. No cherry red spot was seen and the macula appeared normal. There were four, small blotlike

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6. This case is reported with the permission of Dr. Robert Feeley and Dr. Robert McQuoid.

hemorrhages about half disk size situated about 2 disk diameters from the disk. There were sheaflike light areas over the veins in two places. The "sheaf" was constricted at the vessel and flared out at right angles on each side. Arteriovenous nicking was present but minimal. The findings on the right were essentially the same, except that there were only two small hemorrhages and the blood vessel changes were slightly less prominent. Vision was entirely absent in the left eye; with glasses it was normal in the right eye.

Examination of the oral cavity revealed edentulous gums and no evidences of inflammation. The tongue showed a scant coat and was slightly reddened. The jaws opened to admit two fingers vertically between the upper and lower incisors of her dentures. No cervical adenopathy or lymphadenopathy elsewhere was noted. The chest was clear to percussion and auscultation. The heart was of normal size and shape to percussion. The heart sounds were of good quality and no murmurs were heard. The abdomen and extremities were normal. Results of neurologic examination were entirely within normal limits.

Roentgen studies of the sinuses, skull and upper part of the gastrointestinal tract showed them to be normal. A roentgenogram showed that the chest was normal except for moderate sclerosis in the aortic arch.

*Laboratory Examination.*—Two voided specimens of urine were normal on routine analysis except for frequent red blood cells in the sediment of one. A catheterized specimen showed only a few red cells in the sediment. Blood studies showed 9 Gm. of hemoglobin per hundred cubic centimeters; red blood cells numbered 3,600,000 per cubic millimeter; white blood cells, 9,100 with a normal differential count and 0 to 2 per cent eosinophils. The nonprotein nitrogen was 42 mg per hundred cubic centimeters. Blood culture showed no growth. The reaction to the Kahn and Hinton tests of the blood was negative as was that of the spinal fluid to the Kolmer-Wassermann test. Lumbar puncture yielded clear and chemically normal spinal fluid under an initial pressure equivalent to 130 mm. of water. The cell count was 3 lymphocytes and 8 red blood cells per cubic millimeter and the protein was 35 mg. per hundred cubic centimeters. Erythrocyte sedimentation rate showed a rapid fall to 33 mm. in twenty minutes on three occasions, each reading also being 33 mm. at the end of an hour. Three weeks after admission it fell to 26 mm. in twenty minutes and 28 mm. at the end of an hour (Cutler method).

*Treatment and Course.*—The course in the hospital was at first uneventful. The headache was easily controlled by the administration of 10 grains (0.65 Gm.) of acetylsalicylic acid twice daily. On the third day in the hospital, she began to see "black spots" before the right eye. These lasted only fifteen minutes and subsided, but they kept recurring. Examination of the eyes revealed no change. The temperature ranged from 98 to 100 F. and the pulse rate from 68 to 90 beats per minute; the respirations were normal. Treatment consisted of amylnitrite inhalations four times daily and administration of nicotine acid 50 mg. four times daily. With this treatment she stated that she felt better. Ferrous sulfate, 2 grains (0.13 Gm.), three times daily, was given for the anemia. Despite treatment she lost an additional 10 pounds (4.5 Kg.) in the first two weeks of her hospital stay. During the entire second week her temperature remained normal. On the fifteenth day in the hospital she became totally blind in both eyes. She was unable to perceive even bright light. Examination revealed no changes except that the vascular changes in the right eye had gradually become more prominent. The broken columns of blood giving the segmented appearance to the veins were not seen again after the first two or three days. A few more hemorrhages, similar to those described, appeared in both eyes during her hospitalization. By the twenty-fifth day in the hospital, when she was discharged, she was just able to detect a bright light shown directly in either

eye. The headache had entirely disappeared. Ophthalmoscopic examination was unchanged. The temperature, after the onset of the total blindness, once again took a swinging course, going as high at 100 F. in the afternoon. At the time of discharge she had lost a total of 40 pounds (18.1 Kg.).

*Follow-up Study.*—This study four months after her admission to the hospital revealed that she had continued to have fever, malaise and anorexia for about a month after discharge. She had lost an additional 10 pounds of weight, making the total loss 50 pounds (22.7 Kg.). More recently she had been asymptomatic except for the blindness, which had not improved. The headache did not recur. About three months after discharge severe cystitis developed with urethral stricture and infection of the neck of the bladder. Treatment with sulfonamide compounds was started but had to be stopped because of nausea and vomiting. Urethral dilatation and irrigations of the bladder with silver nitrate cleared up these symptoms satisfactorily. She also had some reactivation of the arthritic symptoms. Examination revealed dilated, equal and immobile pupils. Ophthalmoscopic examination revealed that the nerve heads were pale and had a definite yellowish hue. The arteries showed sclerosis consistent with her age, the veins were normal, and there was slight arteriovenous compression. No hemorrhages were seen. The results of the remainder of the physical examination were unchanged.

Six months after discharge from the hospital and eight months after the onset of the disease she was seen again. She had remained well since her last visit. The mild arthritic pains were easily controlled by salicylates. With loss of sight her appetite remained poor and she failed to gain weight. She moved about little because of her poor vision. Vision had improved slightly, especially on the left; she could now distinguish grossly between light and dark without the light being shown directly into the eyes. Examination revealed that the left pupil was slightly smaller than the right and seemed to have some tone. The right pupil remained dilated and immobile. The nerve heads now showed mottling with almost black pigment over the lower halves. Otherwise observations were unchanged. Treatment since discharge from the hospital has been with administration of large doses of vitamins B complex and C.

*CASE 27.—History.*—B. W., a 64 year old housewife, entered the hospital on Aug. 6, 1946 complaining of pain across the forehead. She had been well until twelve weeks before admission, when she noticed a mild bilateral frontal headache. This was gradually progressive in severity and was only temporarily relieved by the usual analgesics. She described the pain as a severe throbbing ache concentrated at the temples. It seemed superficial and the skin over the temples and upper part of the forehead was sensitive to touch, especially along a swollen and nodular "vein" on each side. There was no hemicrania, nausea, vomiting, rhinorrhea or postnasal discharge. For ten days prior to admission she had had difficulty opening and closing her mouth because her "jaws seemed to stick." She was unable to open her mouth more than one fingerbreadth. For the past week the skin of the upper third of the face seemed puffy, especially about the right eye. There had been smarting pains in the eyeballs, especially on movement of the eyes. This was more marked on the right than on the left. The eyes seemed more comfortable closed and in a darkened room. She had felt slightly feverish throughout her illness but had not taken her temperature. She thought she had lost a few pounds in weight.

The past history, family history and review of systems were noncontributory.

*Examination.*—Examination revealed a well developed and well nourished white woman complaining of severe headache. The skin was clear and not flushed. There

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7. Dr. Henry C. Knowlton permitted us to report this case.

was evidence of some recent loss of weight. The temporal arteries on both sides were swollen, firm and tortuous. There were multiple small nodules 2 or 3 mm. in diameter along the course of the arteries, usually at a turn in their tortuous course. Redness and nonpitting edema extended about 1 cm. to each side of the arteries along their entire course anteriorly. This whole area was tender to touch, especially over the nodules, where the tenderness was exquisite. Tenderness seemed to increase toward the origin of the arteries and was maximum over the temporomandibular joints. There was no tenderness over the mastoids or sinuses. The pupils were equal, round and regular and reacted well to light and in accommodation. The scleras and conjunctivas were clear. There was constant lacrimation of the right eye. The lids were voluntarily kept partly closed. Ophthalmoscopic examination revealed clear media and normal-appearing retinas. The vessels were normal and the nerve heads well outlined. There were no hemorrhages, exudates or arterio-venous nicking. Examination of the oral cavity was impeded by the inability of the patient to open her mouth more than 2.5 cm. between the upper and the lower incisors. No pharyngeal or tonsillar inflammation could be seen. There was slight nonpitting edema with redness of the upper third of the face, especially on the lateral aspects of the mandibular angles and extending up over the upper part of the forehead; this was more noticeable on the left. Cervical lymph nodes could not be palpated and adenopathy was not found elsewhere. Motion of the neck was normal. The pulmonary fields were clear to percussion and auscultation. The heart showed a normal rate and rhythm, with a grade pulmonic systolic murmur. The blood pressure was 150 mm. of mercury systolic and 80 mm. diastolic. No masses or viscera were palpated in the abdomen. There was a well healed appendectomy scar in the right lower quadrant. The extremities were normal. Cranial nerve function, reflexes and motor and sensory power were all normal.

Roentgen examination of the chest and temporomandibular joints showed no abnormalities. Roentgenograms of the anterior lower teeth showed moderate alveolar absorption but otherwise these teeth were normal; the remaining teeth were absent.

*Laboratory Examination.*—A catheterized specimen of urine was normal on routine analysis. The hemoglobin was 10.4 Gm. per hundred cubic centimeters; the red blood cells numbered 3,550,000 per cubic millimeter; the white blood cells, 11,000, with a normal differential count. No more than 4 per cent eosinophils were seen on any one count. The erythrocyte sedimentation rate was 18 mm. in 20 minutes and 29 mm. in 60 minutes (Cutler). Kahn and Hinton tests of the blood gave negative results. Blood nonprotein nitrogen was 30 mg. per hundred cubic centimeters.

*Treatment and Course.*—During hospitalization the temperature took a swinging course between 98.6 and 100 F., reaching 99 F. just before discharge, after a thirteen day stay in the hospital. The pulse rate varied from 90 to 120 beats a minute. The respiratory rate was normal. The patient usually required three 1/8 grain doses (0.008 Gm.) of morphine sulfate per day to control her headache. On the morning of the second day she complained of being unable to see with the right eye. Her vision returned to normal in a few hours, however, and the transient blindness did not recur. She insisted on having the room darkened and spent most of her time lying in bed with her eyes closed though not sleeping. She ate poorly and complained that eating hurt her at the temporomandibular joints.

A diagnosis of bilateral temporal arteritis was made on admission and symptomatic therapy was advised. The hospital course, however, seemed to indicate that some more active measures for the relief of pain would be required. She was seen, therefore, on the sixth hospital day by Dr. A. Price Heusner who advised section



of the temporal arterics. Accordingly, under local anesthesia with procaine hydrochloride 3 cm. vertical incisions were made over the temporal arteries successively, exposing normal auriculotemporal nerves, hard, pale, slightly pulsatile and extremely tortuous temporal arteries and swollen tortuous veins. Of each artery 1.5 to 2 cm. was isolated between ligatures and removed together with the veins and perivascular sympathetic nerves. The wounds were closed by galeal sutures alone on the left and by galeal and skin sutures on the right side. The patient experienced slight nausea and vomiting after the second side was completed. Otherwise she felt well throughout the procedure and returned to the ward in excellent condition.

Postoperatively her course was remarkable only for dramatic relief of her symptoms. There were transient swelling and redness of the left eye from the second to the fifth postoperative day. There was also some pain in the jaws, for which morphine was given on the evening of the first and second postoperative days. The headache, tenderness and swelling disappeared, and she was discharged on the seventh postoperative day, thirteen days after admission.

*Follow-up Study.*—When seen one month after operation she was completely free of headache and other local symptoms. She was able to carry on all of her normal activities without discomfort. She still had an occasional low grade rise in temperature in the afternoon. She had not regained her normal appetite though she had gained 1 pound (0.5 Kg.) in weight. There had been no further symptoms or signs referable to the eyes. Her legs felt somewhat stiff but she attributed this to enforced rest in bed. A few days before examination she had herpes labialis and aphthous stomatitis, which were almost healed. The radicles of the sectioned temporal arteries were still nodular and firm but were not tender. The overlying skin was still slightly discolored. Neurologic and ophthalmologic examinations gave entirely normal results. Visual acuity was 20/200 in both eyes without glasses, corrected to 20/20 on the right and 20/30 on the left with glasses.

Two and a half months postoperatively and five and a half months after onset of her disease she was again seen. The fever had subsided and there had been a marked improvement in her appetite and a general feeling of well-being. She last noted fever on October 15 and had felt well since that time, making the total duration of her disease five months. The temporal artery radicles were not tender and were less nodular. Vision and optic fundi were normal. The remainder of the examination gave unchanged results. She was considered fully recovered.

*Pathologic Examination of Biopsy Specimens of Temporal Vessels.*—Sections of vessels fixed in formaldehyde were stained with hematoxylin and eosin and with Verhoeff's elastic tissue stain. Multiple sections taken at various levels of the 2 cm. sections of the temporal vessels revealed a variety of pathologic changes. Most of the sections (fig. 1) revealed one or two large arterics with their venae comites and periarterial nerves bound together in a moderately dense granulomatous tissue. Scattered throughout this dense stroma are numerous small arterics, veins and nerves surrounded by a moderately dense infiltration of inflammatory cells. The density of this infiltrate varies considerably in different areas. There are many lymphocytes present and they predominate in the cellular reaction. In some places they are congregated in small foci. Occasionally they form cuffs about some of the small vessels. In most regions they are diffusely scattered throughout the stroma. Fibroblasts, histiocytes, epithelioid cells, eosinophils and occasional multinucleated giant cells are all scattered throughout the granulomatous tissue. Many of the multinucleated giant cells have a high ratio of nucleus to cytoplasm (figs. 2, 3, 4, and 5). Some of them contain as many as 30 nuclei (fig. 4).

Scattered throughout the granulomatous stroma are many small capillaries. Where these capillaries are most abundant there is considerable hemorrhage into

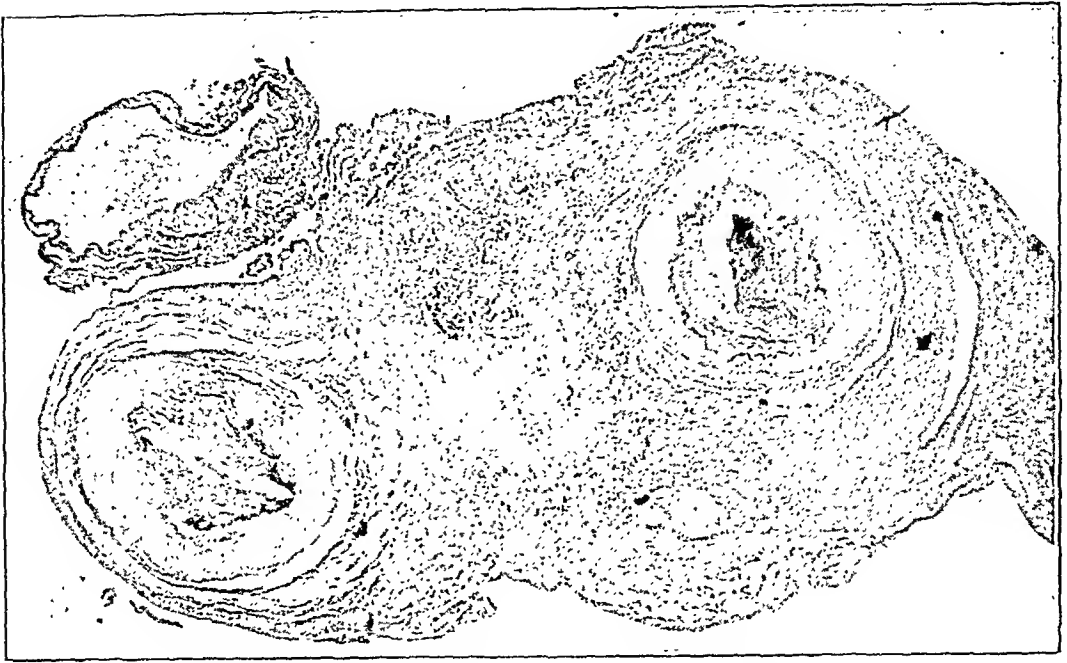


Fig. 1 (case 2).—Right temporal artery and venae comites (Verhoeff's elastic tissue stain, counterstained with Van Gieson's connective tissue stain). The arteries and veins are bound together by dense granulomatous tissues. There is reduplication of the internal elastic lamina of the arteries. The intima is thickened. There is a thrombus in the lumen of one artery. Note the eccentric thickening of the vein at the upper left side. The phlebitis involves that portion of the vein which lies adjacent to the periarterial granulomatous process. The detailed structure of this vein is shown in figure 9.

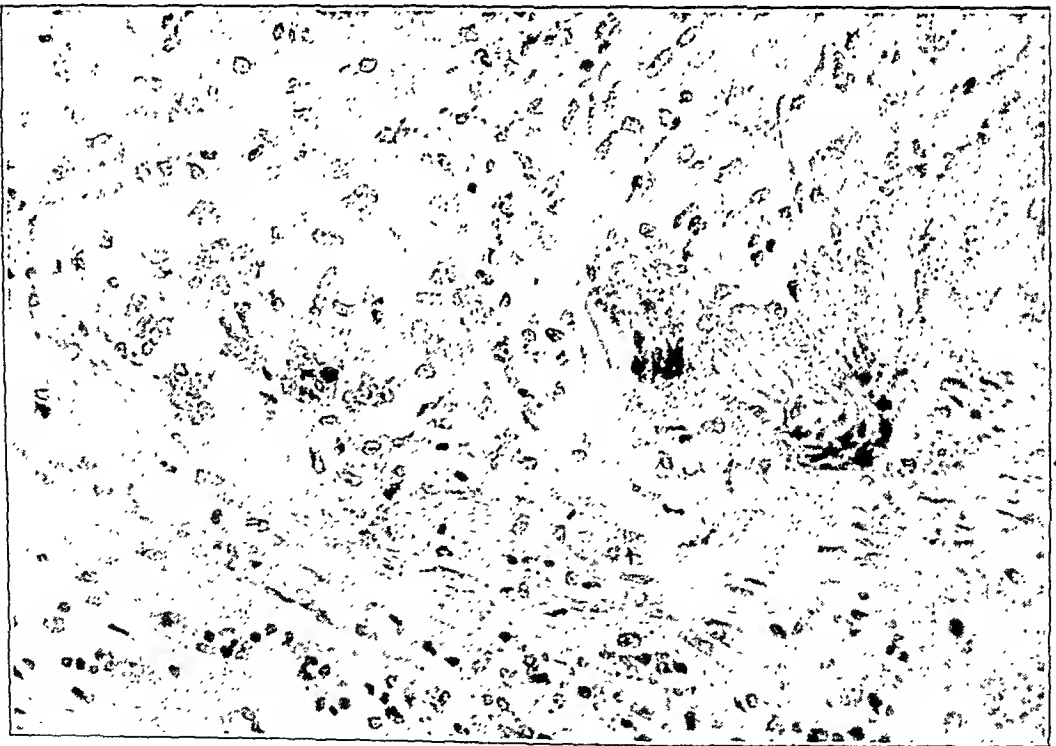


Fig. 2 (case 2).—Left temporal artery (hematoxylin and eosin stain); granulomatous reaction showing irregular distribution of epithelioid cells, lymphocytes, fibroblasts and multinucleated giant cells with irregular contours, vacuoles and apparent fusion of giant cells.

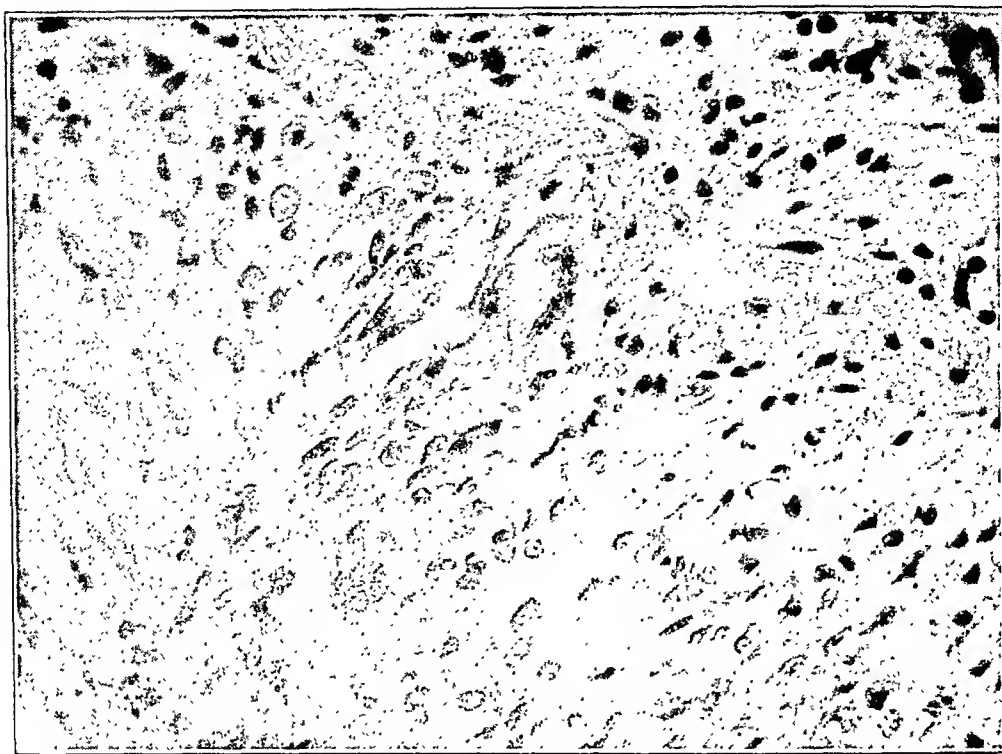


Fig. 3 (case 2).—Right temporal artery (hematoxylin and eosin stain); granulomatous reaction composed of fibroblasts, epithelioid cells and mononuclear cells. Note multinucleated giant cells with irregular contours and peripheral distribution of nuclei.

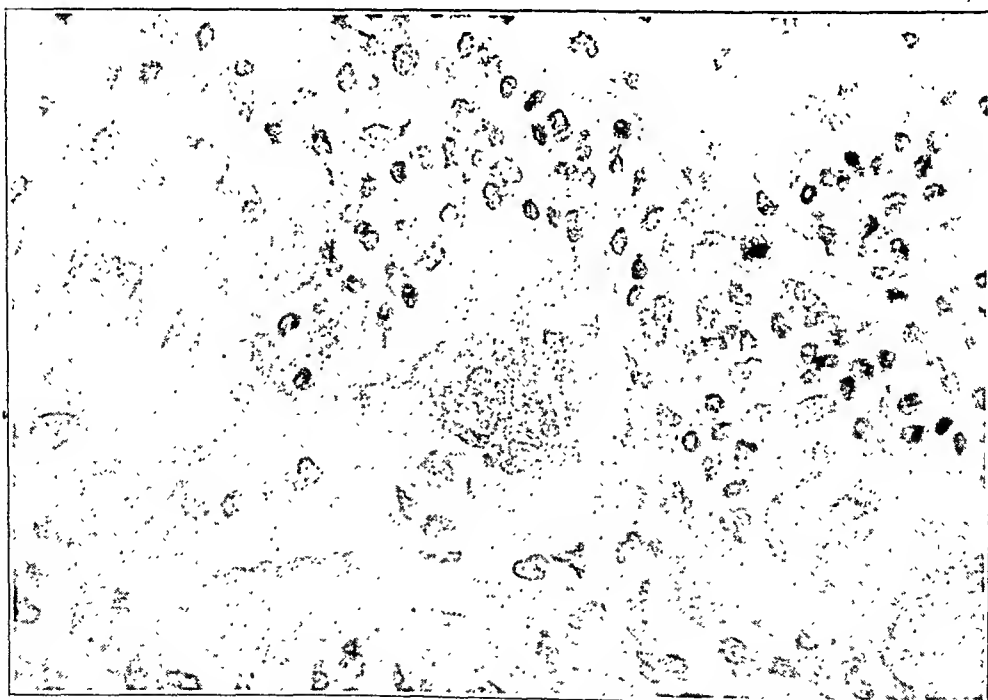


Fig. 4 (case 2).—Left temporal artery (hematoxylin and eosin stain); large multinucleated giant cell containing over 30 nuclei, lying adjacent to the internal elastic lamina and surrounded by mononuclear cells.

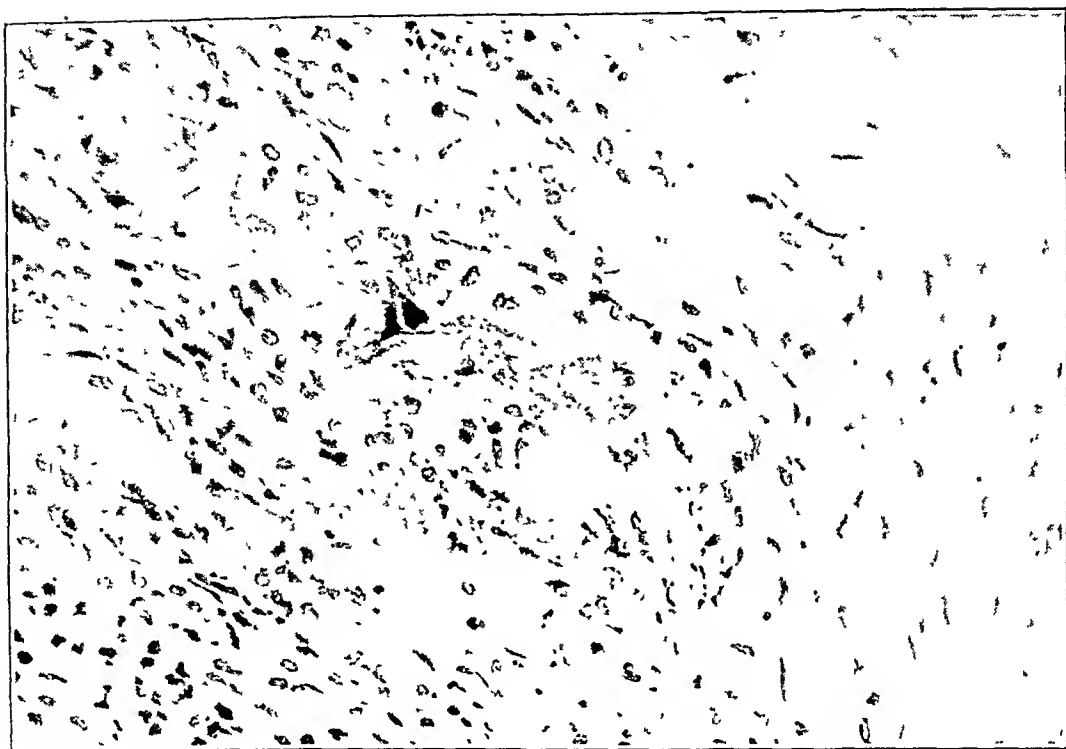


Fig. 5 (case 2).—Left temporal artery (hematoxylin and eosin stain); foreign body giant cell reacting to degenerating elastica.

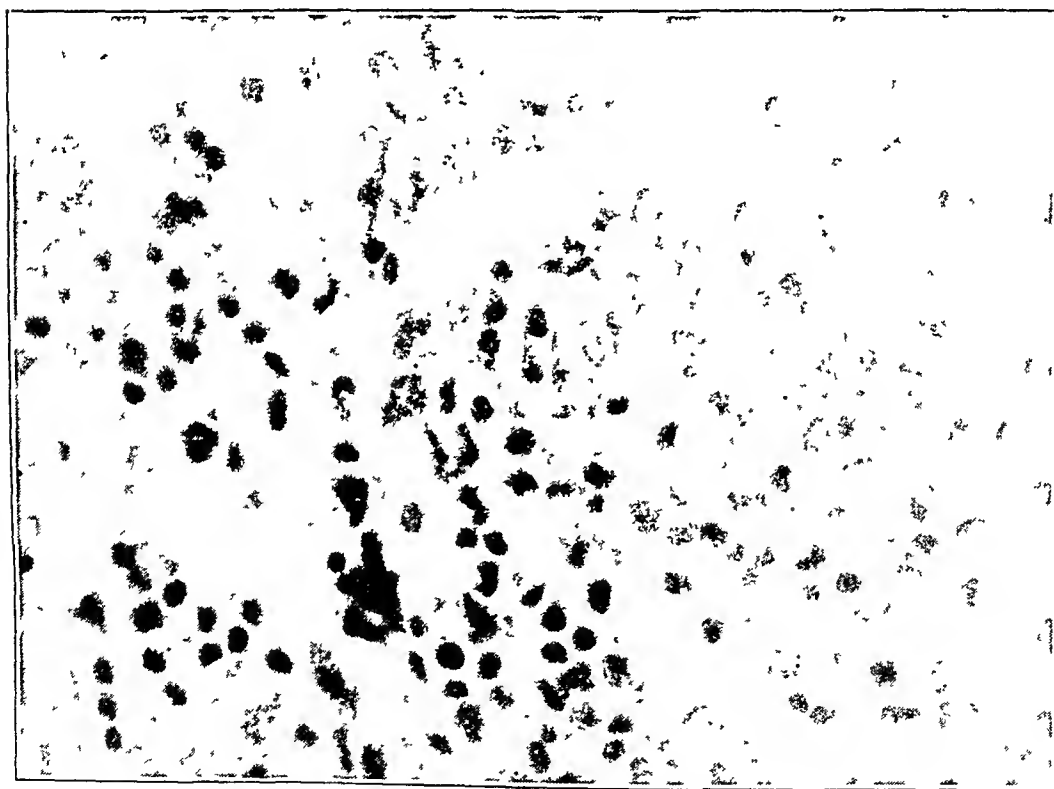


Fig. 6 (case 2).—Left temporal artery (hematoxylin and eosin stain); granulomatous nodule in media. Note the hyalinization of the nutrient vessel at upper right side. Mononuclear cells predominate throughout the lesion.

the surrounding tissue. The endothelial cells lining these capillaries are moderately swollen and in some there is a double layer of cells. Occasional mitotic figures in these endothelial cells are evidence of active proliferation. Numerous polymorphonuclear leukocytes and eosinophils are found in the lumens of the vasa vasorum. Some of these vessels show a loss in the continuity of the endothelial lining and a concomitant infiltration of polymorphonuclear leukocytes in the walls. Some of them have thickened hyalinized walls (fig. 6). The lumens of some contain hyaline thrombi. An occasional dilated lymphatic vessel is observed. Scattered throughout the granulomatous stroma are numerous small sharply circumscribed nodules usually showing some necrosis and containing lymphocytes, histiocytes, occasional eosinophils, an occasional polymorphonuclear leukocyte and a few scattered cells

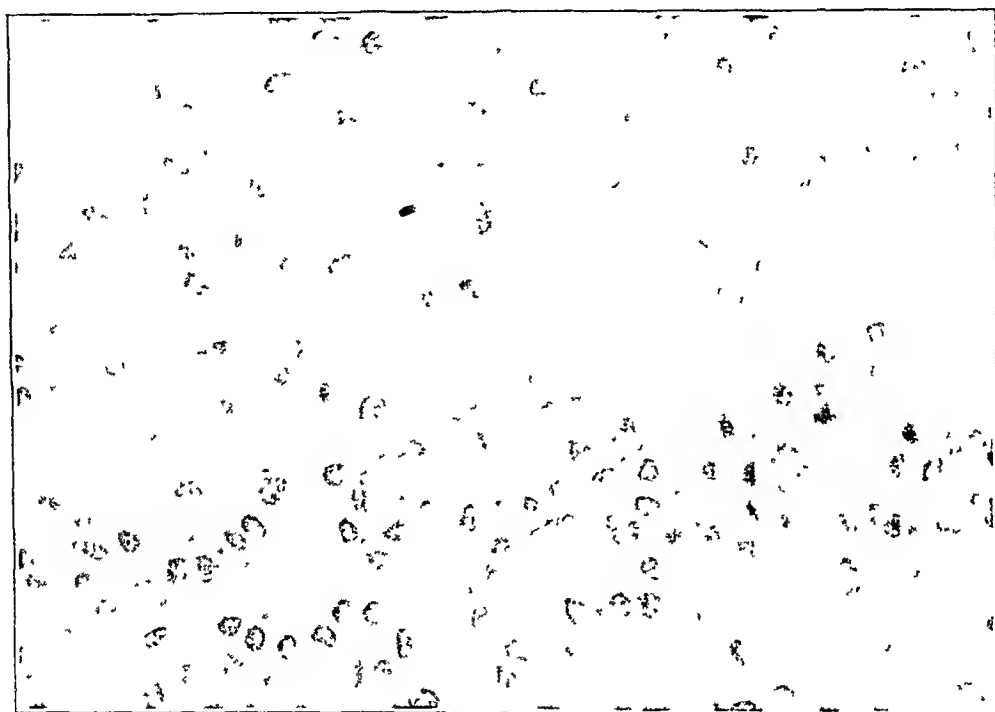


Fig. 7 (case 2).—Left temporal artery (hematoxylin and eosin stain): portion of granulomatous reaction showing numerous eosinophils. Note the granules in the cytoplasm of the eosinophils. The small deeply staining cells are lymphocytes.

undergoing karyorrhexis (figs 6 and 7). None of these nodules have the architectural pattern of tubercles.

In those sections where the inflammatory reaction is least marked there appears to be a fairly sharp demarcation between the granulomatous tissue and the adventitia of the large arteries and veins (fig. 8). Where the inflammatory reaction is most marked the granulomatous tissue appears to replace the adventitia and, in some areas, to replace a large part of the vessel wall. This is particularly true of the veins which lie adjacent to an active focus. Here the wall of the vein adjacent to the artery is at times almost completely replaced by granulomatous tissue while the opposite wall remains intact (fig. 1). In some of the involved veins the muscularis and intima contain numerous small vessels distended with erythrocytes. There are numerous small scattered areas of hemorrhage. In some of the veins

hyalinized vasa vasorum penetrate the intima (fig. 9). In several of the veins there is an eccentric thickening of the intima with an infiltration of lymphocytes, histiocytes, epithelioid cells and occasional polymorphonuclear leukocytes. The endothelial lining is disrupted in some areas and organizing thrombi are attached to the intima.

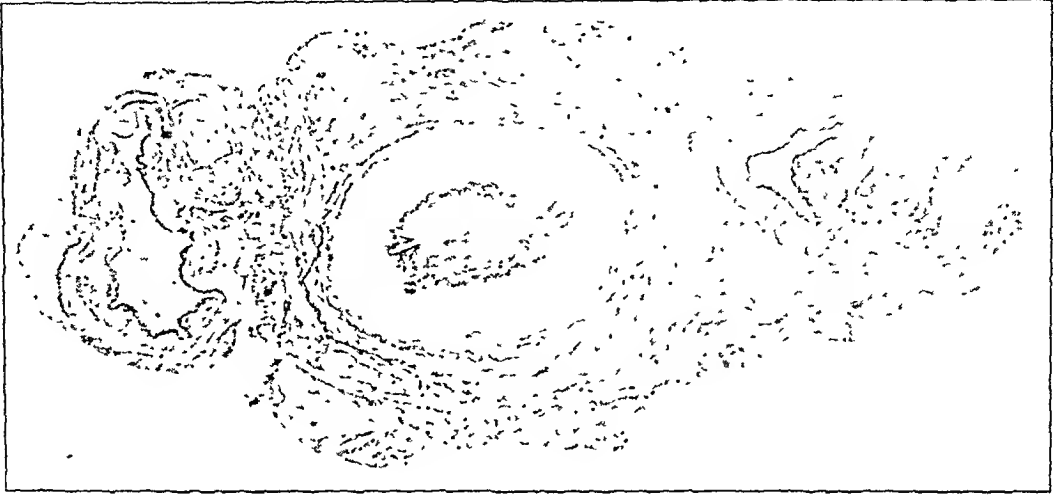


Fig. 8 (case 2).—Right temporal artery and venae comites (Verhoeff and Van Gieson stain); relatively healthy segment of artery with little evidence of granulomatous process, some reduplication of internal elastic lamina and slight intimal thickening. Venae comites are well preserved.

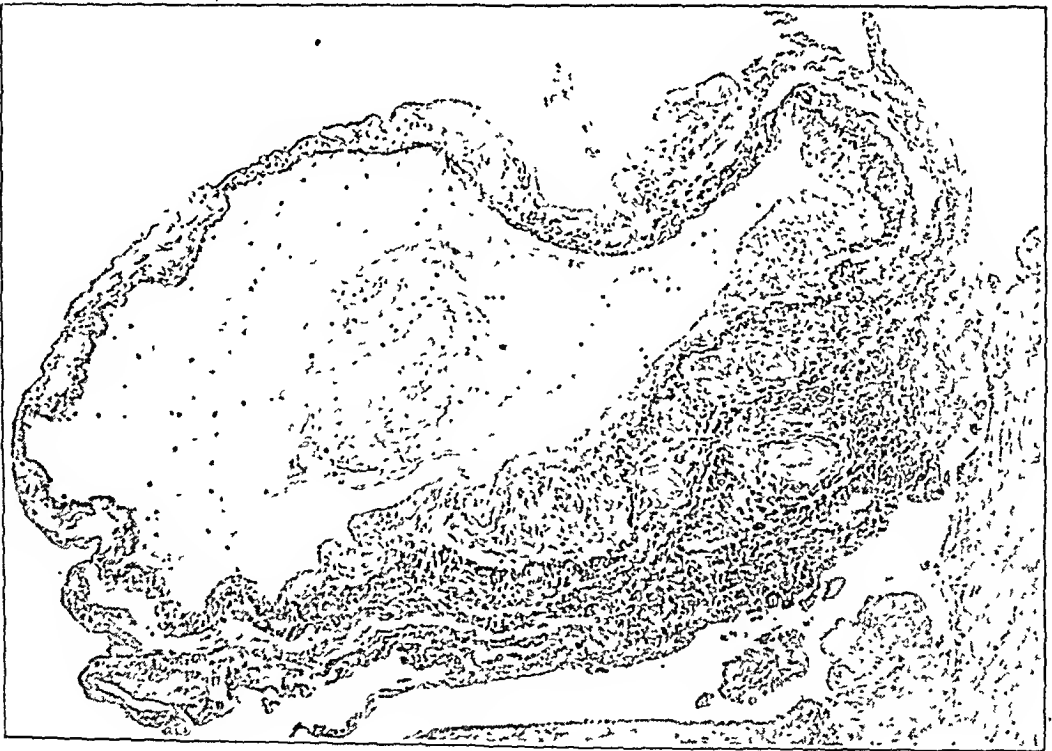


Fig. 9 (case 2).—Right temporal vein (Verhoeff and Van Gieson stain); high power enlargement of vein shown in figure 1. Note the granulomatous reaction adjacent to the periarterial structures. The vasa vasorum are numerous and hypertrophied and penetrate the thickened intima. The opposite wall remains intact.

In some sections of the larger arteries the muscularis is essentially unaltered (fig. 8). In other sections there are sharply circumscribed granulomatous nodules replacing either a portion of, or the entire thickness of, the media (fig. 10). These nodules are similar to those described in the periadventitial tissues. They contain areas of necrosis, lymphocytes, histiocytes, epithelioid cells and occasional eosinophils and polymorphonuclear leukocytes. In one of these nodules there are numerous multinucleated giant cells. In some sections the media of the artery is partially replaced by pale acellular collagenous tissue which is surrounded by a variety of inflammatory cells (fig. 11). The media shows a focus of arteritis at the site of origin of smaller branches (fig. 12).

In most of the arteries the internal elastic lamina is badly damaged (figs. 1, 10, 12, 13 and 14). There is marked fragmentation of the elastica and reduplication is

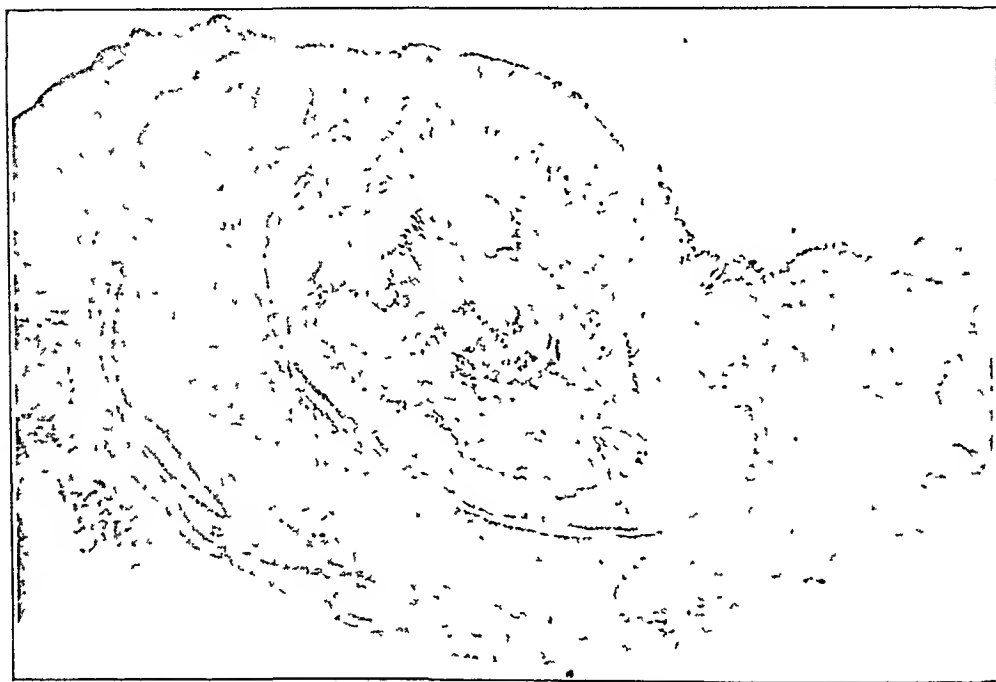


Fig. 10 (case 2) —Right temporal artery (Verhoeff and Van Gieson stain). This section of artery is diffusely involved by the granulomatous process. At the upper right side the muscularis is thin and necrotic. The elastica is partially destroyed. This represents a potential site for the development of an aneurysm. The lumen is almost occluded by thrombus.

frequently seen. In the area of the most intense inflammatory reaction the elastic lamina is missing (fig 10). In many areas the elastic fibers are swollen, with the formation of sharply defined basophilic deposits resembling calcium (figs. 5, 8 and 14). Multinucleated giant cells are numerous in these areas. In most of the sections there is a fairly marked intimal thickening (figs. 10, 13 and 14). Where the muscularis is least involved the thickened intima consists of moderately dense collagenous tissue and the endothelial lining appears intact (fig 8). Where the media is extensively involved by the granulomatous process the intima is diffusely infiltrated with inflammatory cells (fig. 10). In these areas the endothelial lining is frequently disrupted and organized thrombi are attached to the intima.

Sections of the left temporal artery reveal extensive granulomatous involvement of the media at one level. There is a loss of continuity of the muscle fibers and

the internal elastic lamina is missing in this region. An aneurysmal outpocketing extends out into the periadventitial granulomatous tissue (fig. 13). There is scattered hemorrhage in the surrounding vessel wall. Sections of the right temporal

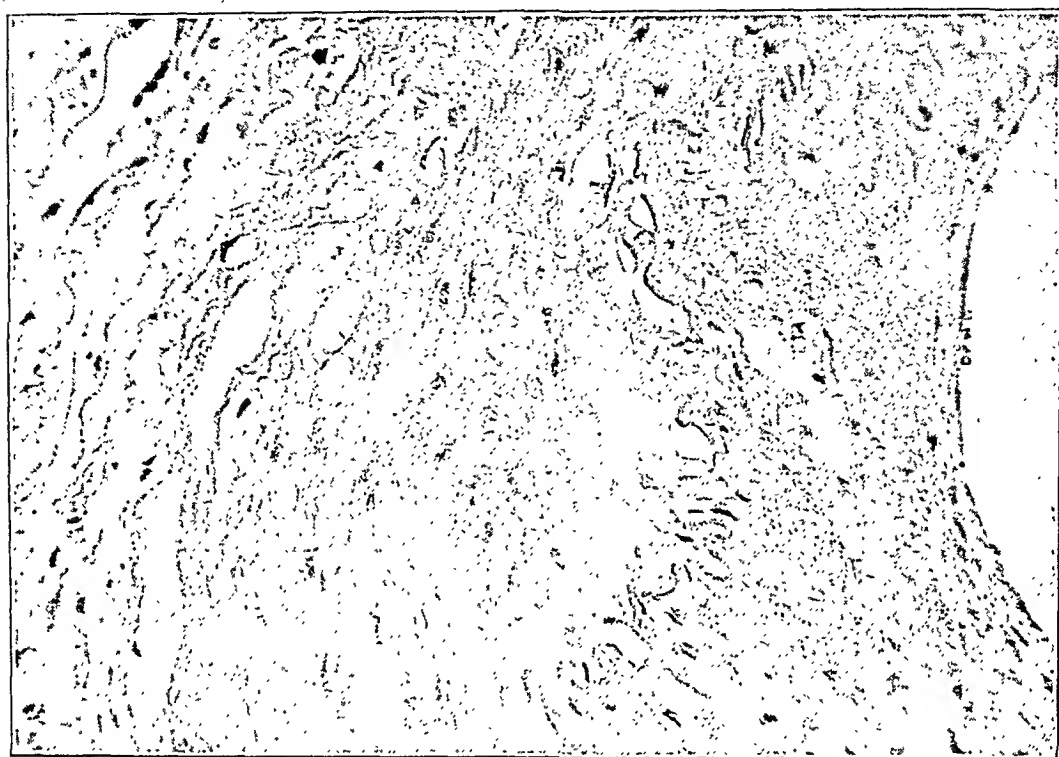


Fig. 11 (case 2).—Right temporal artery (hematoxylin and eosin stain). Pale acellular collagenous tissue external to internal elastic lamina represents medial necrosis with minimal cellular response.



Fig. 12 (case 2).—Left temporal artery (Verhoeff and Van Gieson stain). Accentuation of granulomatous process at the site of bifurcation of the artery.





Fig. 13 (case 2).—Left temporal artery (Verhoeff and Van Gieson stain); a dissecting aneurysm which penetrates the adventitia of the artery. Note the great inflammatory reaction at this level. There are several "weak spots" in the media.

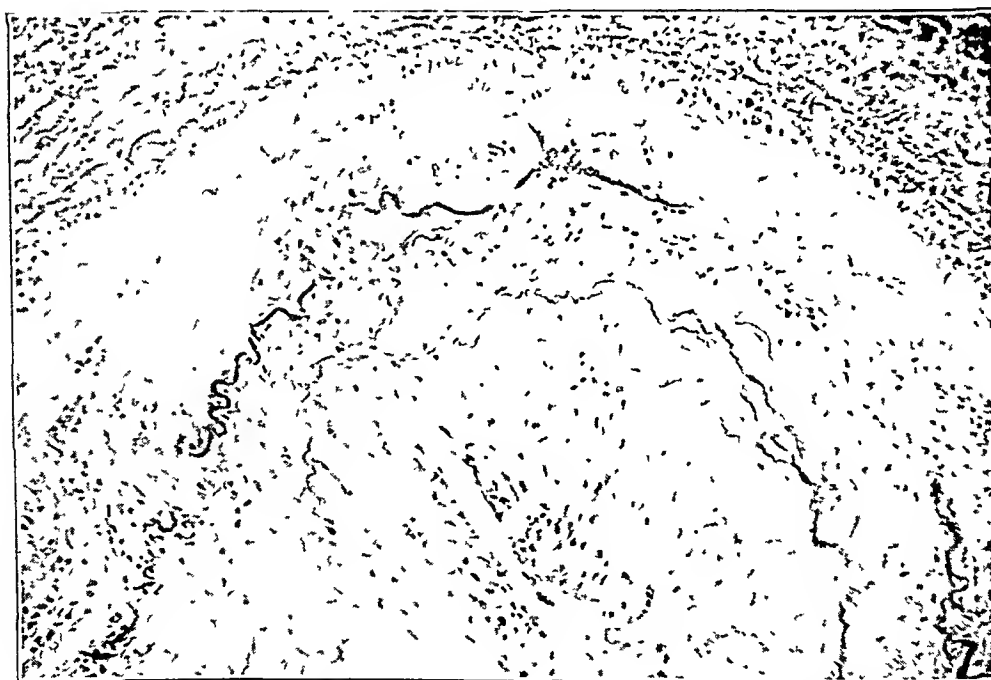


Fig 14 (case 2) —Left temporal artery (Verhoeff and Van Gieson stain). The intima is markedly thickened. The lumen is almost obliterated. Numerous multi-nucleated giant cells are found external to the fragmented elastica. The media reveals necrosis with minimal cellular reaction.

artery reveal a similar destruction of the media and elastica with less marked outpocketings from the lumen (fig. 10). No deposition of hemosiderin or phagocytosis of erythrocytes is found in any of the sections.

CASE 3<sup>s</sup>.—J. McC., a 79 year old man, was admitted to the hospital on March 5, 1947 because of headaches. He had been well except for "prostatism" relieved by perineal prostatectomy about a year prior to admission. Ten weeks before admission there rather suddenly developed a severe, throbbing, and constant bitemporal headache. His scalp was so tender that he could not comb his hair. Five weeks before admission he noticed occasional blurring of vision and ten days before admission he had diplopia. Shortly after admission he became completely blind in the right eye.

Examination revealed tortuous, swollen, tender and red temporal arteries bilaterally with discoloration and induration of the overlying skin. Ophthalmoscopic examination revealed a normal condition on the left. On the right both arteries and veins were narrow; there was a large flame-shaped hemorrhage over the disk; the retina showed numerous petechiae and some diffuse edema. The remainder of the examination gave essentially normal results.

Laboratory study revealed: hemoglobin, 54 per cent, 3,250,000 red blood cells per cubic millimeter and 10,400 white blood cells, with a normal differential count. There were 2 per cent eosinophils. The erythrocyte sedimentation rate (Westergren) was 115 mm. per hour. The urine showed albumin (1+), 5 to 10 red cells and 10 to 15 white cells per high power field in the sediment. The spinal fluid was under normal pressure and chemically and serologically normal, with 28 mg. protein per hundred cubic centimeters.

During his stay in the hospital he had a low grade fever. A biopsy specimen of the temporal artery on the right was taken with the patient under local anesthesia and caused relief of the headache almost immediately. The low grade fever and blindness persisted.

Pathologic study of the biopsy specimen of the temporal artery revealed active arteritis characterized by scarring of the adventitia, active chronic granulomatous inflammation of the media with the development of multinucleated giant cells, and obliterative endarteritis in which there was mucoid intercellular deposit. The pathologic diagnosis was "temporal arteritis."

CASE 4.—A. S., a 67 year old housewife was admitted to the hospital on March 8, 1947 because of headache and blindness. She had been well until November 1946 when general weakness led to study of the blood. Anemia, which was not further clarified, was found and intramuscular injection of liver extract was said to have corrected the weakness and the anemia. In December 1946 severe and constant headache developed rather suddenly over the vertex. This soon shifted to a severe, throbbing, constant bitemporal ache. Fever with a temperature of 101 F. was noted. Two weeks before admission she noticed a "smoke screen" before the right eye and became blind in that eye. She was totally blind in this eye for a week and then vision improved to the point where she could distinguish objects grossly.

Examination revealed tortuous, swollen, red and tender temporal arteries bilaterally with discoloration and slight induration of the overlying skin. Ophthalmoscopic examination of the left eye gave normal results for her age. The right optic disk was pale and there was some edema of the retina, but no hemorrhages were seen. The remainder of the examination gave essentially normal results.

Laboratory study revealed: hemoglobin, 60 per cent, 3,150,000 red blood cells per cubic millimeter and 9,700 white blood cells, with a normal differential count. Eosinophils were not seen. Routine urinalysis gave entirely normal results. The

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8. Dr. Sigfried Thannhauser permitted us to report this case.

erythrocyte sedimentation rate (Westergren) was 132 mm. per hour. Roentgenograms of the chest, skull and gastrointestinal tract showed them to be normal.

During her stay in the hospital she had a low grade fever. Those observing her felt that there was definite improvement in the vision of her right eye even during a short period of observation. Her headache was not excessively severe, and she was discharged on symptomatic therapy.

CASE 5.—E. H., a 75 year old widow, was admitted to the hospital on March 25, 1947 because of headaches. She had been well until two months prior to admission, when severe, constant, throbbing bitemporal headache developed. She had tenderness of the scalp with some swelling in the temporal regions and of the left ear. The swelling had subsided but the headache persisted, especially on the left. There were no visual symptoms.

Examination revealed a swollen, tortuous and tender left temporal artery. On the right the temporal artery was hard, "stringlike," and without pulsation. There were slight induration and discoloration of the overlying skin. Ophthalmoscopic data were normal for her age. The remainder of the examination gave normal results.

Laboratory study revealed: hemoglobin, 78 per cent, 4,310,000 red blood cells per cubic millimeter and 10,000 white blood cells, with a normal differential count. There was 1 per cent of eosinophils. The erythrocyte sedimentation rate (Westergren) was 37 mm. per hour. Routine urinalysis gave entirely normal results. Roentgenograms of the skull showed slight hyperostosis frontalis interna.

It was thought that her disease was subsiding spontaneously. She was therefore discharged on symptomatic therapy.

#### SUMMARY OF THE REPORTED CASES

The five cases reported seem to fulfil the essential criteria of the disease entity temporal arteritis. Four of the patients were women and all were within the age range of previously reported cases. The typical systemic symptoms of fever, malaise, anorexia, loss of weight and weakness were present in all. All showed tenderness, swelling, redness and nodularity of the temporal arteries bilaterally. In case 1 the rapid erythrocyte sedimentation rate, the great and sustained loss of weight, and the microscopic hematuria suggested the possibility of diffuse arterial disease. The patient recovered, however, and is now—twelve months after the onset of the disease—reasonably well. She has had persistent blindness which seems to be improving slightly. She has failed to regain weight but does not eat well because of the loss of zest for food incident to loss of vision. Her condition at present would seem to rule out active generalized arterial disease.

Case 2 seemed to follow a typical course, including the dramatic relief of headache and local symptoms afforded by section of the temporal arteries. Systemic symptoms persisted for about two months post-operatively and then subsided. This probably represents simply the normal course of the disease, only the local symptoms being benefited by operation. Transient unilateral blindness occurred in this case before operation but disappeared in a few hours without therapy. Examination

of the biopsied vessels revealed the occurrence of secondary phlebitis and arterial aneurysm; the latter has not been described previously as present in temporal arteritis.

Case 3 is typical and also demonstrates the relief of local symptomatology which biopsy affords. Case 4 is of particular interest in that there was complete blindness in one eye for a week with unusually complete return of vision in that eye. As a rule blindness of more than a few hours' duration in this disease has been permanent. Case 5 demonstrates a mild but typical case of temporal arteritis with the disease apparently confined to the temporal arteries.

The essential data of all the cases reported to date have been summarized in table 1. This includes the 43 cases found in the literature and our 5 cases. Analysis of the data thus presented reveals the definite uniformity of the clinical features of the disease. These clinical features are presented for the sake of brevity in table 2.

The essential data concerning 9 other cases similar to, and in some cases, perhaps identical with, temporal arteritis are presented in table 3. These cases have been excluded from the temporal arteritis group. The case reported by Paviot, Chevallier, Guichard and Damez<sup>9</sup> was clinically indistinguishable from temporal arteritis. A mitral heart murmur was found during the course of the disease and the patient was treated effectively with salicylates, which led the authors to believe that all his symptoms were rheumatic manifestations. Biopsy was not done, and this case has been excluded only because of insufficient data. Similarly Chavany's<sup>10</sup> case was, from the data given, indistinguishable from temporal arteritis, and he implied that other cases had been seen. The data were inconclusive, however, and the case was therefore excluded. Barnard<sup>11</sup> has reported a case with autopsy observations consisting of arteritis of the coronary, cerebral and retinal arteries, which was histologically similar to that of temporal arteritis. Although tubercle bacilli were not demonstrated, Barnard believed the disease to be tuberculous arteritis. Headache and "erysipelas of the face" were mentioned clinically but pathologic data on the temporal arteries were not given, and hence this case has been excluded. The mesaortitis described in the cases of Sproul and Hawthorne<sup>12</sup> and the "giant cell arteritis" described by Gilmour<sup>13</sup> have been referred to as being similar to temporal arteritis<sup>13a</sup>

9. Paviot, J.; Chevallier, R.; Guichard, A., and Damez, M.: *Lyon med.* **154**:45-51 (July 15) 1934.

10. Chavany, J. A.: *Presse méd.* **44**:347-348 (Feb. 29) 1936.

11. Barnard, W. G.: *J. Path. & Bact.* **40**:433-436 (May) 1935.

12. Sproul, E. E., and Hawthorne, J. J.: *Am. J. Path.* **13**:311-323 (March) 1937.

13. Gilmour, J. R.: *J. Path. & Bact.* **53**:263-267 (Sept.) 1941.

13a. Cooke and others.<sup>2</sup> Chasnoff and Vorzimer.<sup>3</sup>

TABLE 1.—*Essential Data on All the Reported Cases of Temporal Arteritis*

No.	Author and Date	Place	Sex and Age	Arteries Affected	First Symptom	Systemic Symptoms	Duration	Treatment	Outcome	Culture
1	Horton, Magath and Brown, 1932 (1)	Minn., U. S.	F, 55	Temporal	Fever, malaise, anorexia	Fever, weakness, malaise, loss of weight	4-6 mo.	Biopsy	Recovered	Actinomyces
2	Horton, Magath and Brown (1)	Neb., U. S.	M, 68	Temporal	Pain in jaws	Usual, also dental sepsis	4-6 mo.	Biopsy	Recovered	Actinomyces
3	McDonald and Moser, 1937 (1)	Ind., U. S.	F, 60	Temporal	Headache	Usual	5 mo.	Lextron, salicylates	Recovered	Staph. aureus
4	Artucio, Munoz and Falcon, 1937 (*)	Uruguay	M, 57	Right temporal	Not stated	Usual, also hypertension	2 mo.	None	Recovered	None
5	Horton and Magath, 1937 (4)	Wis., U. S.	F, 69	Temporal	Systemic	Usual	4-6 mo.	Iodides, acetylsalicylic acid, biopsy	Recovered	Neg.
6	Horton and Magath, 1937 (4)	Wis., U. S.	F, 75	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
7	Horton and Magath, 1937 (4)	Iowa, U. S.	M, 72	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
8	Horton and Magath, 1937 (4)	Ore., U. S.	M, 65	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
9	Horton and Magath, 1937 (4)	Minn., U. S.	F, 68	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
10	Jennings, 1938 (23)	England	F, 66	Temporal, retinal, (?) radial and foot	Systemic and head-ache	Usual, pain in limbs	18 mo.	Biopsy	Blind Well	None
11	Jennings, 1938 (23)	England	F, 72	Temporal	Systemic	Usual	Some wks. each side	None	Recovered	None
12	Bain, 1938 (32)	England	F, 71	Temporal	Systemic and pain in neck	Usual, sore throat, disoriented	1 month	Azorsulfamide	Rheumatism	None
13	Thevinaud, 1939 (33)	France	M, 66	Temporal, retinal	Blindness	Usual, lime burns to eyes	Few months	Biopsy	Recovered	None
14	Dick and Freeman, 1940 (16)	Ill., U. S.	F, 65	Temporal, retinal, left, (?) occipital	Systemic	Usual	4 mo.	Sulfanilamid	Biopsy	Blind, o. s. Strep. viridans
15	Dick and Freeman, 1940 (16)	Ill., U. S.	F, 76	Temporal	Headache	Usual, diplopia weakness, pains in joints	13 mo.	Sulfanilamide	Recovered	None

\*\*Artucio, H.; Munoz, M., and Falcon, C. M.: Personal communication cited by Horton and Magath.

†Bain, C. W. C.: Lancet 1:517 (Feb. 26) 1938.

‡Thevinaud, M.: Bull. et mém. Soc. d. chir. de Paris 31:136-137 (Feb.) 1939.

No.	Author and Date	Place	Sex and Age	Arteries Affected	First Symptom	Systemic Symptoms	Duration	Treatment	Outcome	Culture
16	Bowers, 1940 (15)	Wash., U. S.	F, 65	Temporal, (2)	Cerebral Headache	Usual—neurosis, hypertension	14 mo.	Vit. liver, iodides, biopsy	Recovered	Gram-coce }
17	Sprague and McKenzie, 1940 (21c)	Canada	M, 66	Both temporal	Headache	Typical	7 mo.	Biopsy	Recovered	None
18	Scott and Maxwell, 1941 (24)	Ky., U. S. A.	F, 70	Temporal and retinal	Weakness, anorexia	Typical, mild diabetic, tender arteries of arm	5 mo.	Biopsy, vit. B	Recovered Blind, O.D.	Neg.
19	Hoyt, Perera and Kauver (25)	Mass., U. S.	F, 51	Both temporal	Headache	Typical	2 mo.	Sulfanilamide, acetophenetidin, biopsy	Recovered	None
20	Hoyt, Perera and Kauver (25)	Mass., U. S.	F, 61	Both temporal	Pains in joints	Typical	12 mo.	Sulfanilimide, biopsy	Recovered, residual arthralgia	None
21	Hoyt, Perera and Kauver (25)	Mass., U. S.	F, 67	Both temporal	Muscle aches	Typical, asthma, hypertension	18 mo.	Biopsy	Recovered	None
22	Sproul, 1942 (29)	N. Y., U. S.	M, 68	Generalized	Headache	Typical, diabetic coronary disease	8 wk.	Supportive	Died, cardiac failure	Nono
23	Schaefer and Sanders, 1942 (31)	Kansas, U. S.	F, 62	Right temporal	Headache, systemic symptoms	Typical delirium	2 mo.	Sanders Oscillating Bed	Recovered	None
24	Murphy, 1942 (34)	N. Y., U. S.	F, 71	Both temporal	Headache, sweats	Usual, vertigo hypertension	6 mo.	Cobra venom, biopsy	Recovered	None
25	Johnson, Harley and Horton, 1943 (27)	Minn., U. S.	F, 61	Temporal and retinal	Systemic	Typical	6 mo.	None	Recovered, Blind, O.S.	Nono
26	Johnson, Harley and Horton, 1943 (27)	Minn., U. S.	M, 75	Temporal and retinal	Headache	Typical, coronary disease	Not stated	None	Recovered, Blind, O.U.	None
27	Johnson, Harley and Horton, 1943 (27)	Minn., U. S.	F, 76	Temporal and retinal	Systemic	Typical	Not stated	Not stated	Under observation	None
28	Chasnoff and Vorzimer, 1944 (3)	N. Y., U. S.	F, 63	Temporal, generalized	Pain, back and groins	Typical, later depression and stupor	14 mo.	Biopsy	Died	None
29	Profant, 1944 (17)	Calif., U. S.	F, 76	Right temporal	Headache	Typical, exacerbation with tooth extraction	11 mo.	Supportive	Recovered	None
30	Profant, 1944 (17)	Calif., U. S.	F, 61	Both temporal	Headache	Typical, angina and hypertension	2 mo.	Sulfathiazole	Recovered	None
31	Brown and Hampson, 1944 (35)	England	M, 61	Temporal	Rheumatic pains	Typical	6 mo.	Biopsy	Recovered	Nono

§Murphy, J. R.: New York State J. Med. 42:2236-2237 (Dec. 1) 1942.

No.	Author and Date	Place	Sex and Age	Arteries Affected	First Symptoms	Systemic Symptoms	Duration	Treatment	Outcome	Culture
32	Shannon and Solomon, 1945 (36)	Mass., U. S.	M, 73	Temporal and retinal	Pain in jaws	Typical	2 mo.	Biopsy	Recovered, blind, O.U.	None
33	Kilbourne and Wolff, 1946 (19)	N. Y., U. S.	M, 68	Temporal	Pain in jaws	Typical, angina pectoris	3 mo.	Biopsy	Recovered, later died of coronary thrombosis	None
34	Cooke and others, 1946 (2)	England	M, 66	Generalized	Blind, O.S.	Typical, inter. claudication, paral. agians	6 mo.	Biopsy	Recovering, blind, O.S., later died	None
35	Cooke and others, 1946 (2)	England	F, 66	Temporal and retinal	Systemic	Typical, scalp eczema	10 mo.	Sulfonamide	Recovering, blind, O.U.	None
36	Cooke and others, 1946 (2)	England	F, 69	Generalized	Pain in thigh	Typical, venous thromboses, polyneuritis	30 mo.	Biopsy	Died, blind	None
37	Cooke and others, 1946 (2)	England	M, 71	Temporal	Headache	Typical	24 mo.	Biopsy	Recovered	None
38	Cooke and others, 1946 (2)	England	M, 69	Temporal, no foot pulses	Pains in joints	Typical, inter. claudication	12 mo.	Biopsy	Recovered	None
39	Cooke and others, 1946 (2)	England	F, 73	Generalized	Systemic	Typical, later disorientation	14 mo.	Biopsy	Blind, died	None
40	Cooke and others, 1946 (2)	England	F, 68	Temporal	Headache, pains in legs	Typical	12 mo.	Biopsy, nicotinic acid	Recovering	None
41	Dantes, 1946 (22)	N. Y., U. S.	F, 55	Temporal (?) rt. dorsalis pedis	Headache	Typical	12 mo.	Biopsy	Recovered	None
42	Gordon and Thurber, 1946 (26b)	N. Y., U. S.	M, 65	Temporal	Pain in thighs	Typical	4 mo.	Biopsy	Recovered	None
43	Curtis, 1946 (26d)	Utah, U. S.	F, 71	Temporal, retinal, (?) cerebral	Headache, vertigo	Typical	3½ mo.	Biopsy	Blind, O.U., Neg. died	Neg.
44	Crosby and Wadsworth	Maine, U. S.	F, 73	Temporal and retinal	Headache	Typical	3 mo.	Amyl nitrate, nicotinic acid	Recovered, blind, O.U.	None
45	Crosby and Wadsworth	Maine, U. S.	F, 64	Temporal	Headache	Typical	5 mo.	Biopsy	Recovered	None
46	Crosby and Wadsworth	R. I., U. S.	M, 79	Temporal and retinal	Headache	Typical		Biopsy	Recovering, Blind, O.D.	None
47	Crosby and Wadsworth	Mass., U. S.	F, 67	Temporal and retinal	Weakness	Typical		None	Recovered, Blind, O.D.	None
48	Crosby and Wadsworth	Mass., U. S.	F, 75	Temporal	Headache	Typical		None	Recovering	None

No. Author and Date Place Sex and Age Arteries Affected First Symptom\* Systemic Symptoms Duration Treatment Outcome Culture

\*\*Shannon, E. W., and Solomon, J.: Bilateral Temporal Arteritis with Complete Loss of Vision, J. A. M. A. 127:647-649 (March 17) 1946.

TABLE 2.—*Clinical Features of Temporal Arteritis (From the Forty-Eight Reported Cases)*

Distribution: England, France, Canada, Uruguay, United States.  
 Age: 55 to 79 years. Average: 67.4 years.  
 Sex: Females: 32 cases. Males: 16 cases. Female/Male ratio: 2/1.  
 Initial symptoms: Local: 25 (5) \*, systemic: 26 (5) \*, blindness: 2.  
 Local symptoms: Headache, pain in adjacent structures, blindness, tender, red nodular temporal arteries, local edema.  
 Systemic symptoms: Malaise, anorexia, fever, loss of weight, weakness.  
 Arteries involved: Temporal 48, retinal 16, generalized 5, (?) cerebral, occipital, radial, dorsalis pedis.  
 Duration: Two to thirty months; average: 7½ months.  
 Treatment: Salicylates, sulfonamide compounds, arsenic, mercury, iodides, vitamins, liver extract, cobra venom, section of arteries.  
 Culture: Actinomycetes, Staphylococcus aureus, Streptococcus viridans; many not done; most were sterile.  
 Outcome: Four died of other causes, 5 of the disease; 6 deaths attributed to the disease; mortality 12.5%.

\*Five patients had both local and systemic symptoms initially.

TABLE 3.—*Essential Data on Cases Similar to but Excluded from Temporal Arteritis*

No.	Author—Date	Place	Sex and Age	Arteries Affected	First Symptom	Systemic Symptoms	Duration	Treatment	Outcome	Culture
1	Pavlot and others, 1934 (9)	France	M, 61	Temporal	Systemic	Fever, pallor, anorexia and mitral-regurgitation	3 mo.	Arsenic, mercury, Salicylates	Recovered	None
2	Barnard, 1933 (11)	England	F, 62	Coronary, cerebral, Retinal	Headache	Blind in one eye, weakness, "crysipelas of face"	10 wk.	None	Died	Neg.
3	Chavany, 1936 (10)	France	F, 63	Temporal	Headache	Fever, loss of weight, rheumatism	Not stated	Not stated	Recovered	None
4	Sproul and Hawthorne, 1937 (12)	N. Y., U.S.	M, 76	Aorta, iliac	Prostatism	None	Prostatism, 3 yr.	Prostatectomy	Died of Pneumonia	None
5	Sproul and Hawthorne, 1937 (12)	N. Y., U. S.	M, 50	Aorta, iliac, carotid	Preordial pain	Congestive heart failure	1 year	Supportive	Died of heart failure	None
6	Gilmour, 1941 (13)	England	F, 23	Aorta and branches of aorta arch	Giddiness, sweats	Neuritis, congestive heart failure, hemoptysis	6 mo.	Supportive	Died	None
7	Gilmour, 1941 (13)	England	F, 59	Aorta, carotid and branches	"Influenza"	Influenza, measles rash, peeling hands and feet, hemiplegia and coma	5 mo.	Supportive	Died	None
8	Gilmour, 1941 (13)	England	M, 63	Aorta, carotids and branches	"Influenza"	Influenza, headache, failing vision, mental dulness	9 mo.	Supportive	Died of "stroke"	None
9	Gilmour, 1941 (13)	England	F, 64	Aorta and major branches	"Influenza"	Influenza, cardiac, abdominal aneurysm enteritis, congestive heart failure	26 mo.	Supportive	Recovering	None



without involvement of the temporal arteries. There are also differences in age group, symptomatology and pathology which justify the exclusion of these cases from the temporal arteritis group.

#### COMMENT

In the fifteen years since Horton, Magath and Brown<sup>1</sup> first described "arteritis of the temporal arteries" as a disease entity 43 cases which seem to warrant this designation have been reported (table 1). Many other cases have undoubtedly been recognized and not reported, yet the disease is relatively rare. Critical analysis of the cases reported to date has established certain facts about the disease. The constancy with which the major clinical features have been found is striking. With the exceptions of the occurrence of blindness and a definite though small mortality, the general clinical picture corresponds closely to the original description of the disease. The symptoms may be conveniently divided into local and systemic. Local symptoms have consisted of severe, throbbing headache with swollen, tender, nodular and thrombosed temporal arteries and pain in the adjacent structures such as the scalp, face, jaws, eyes and temporomandibular joints. Systemic symptoms of fever, malaise, weakness, anorexia and loss of weight have appeared almost constantly. The initial complaints were about equally divided between local and systemic; 26 patients presented themselves with systemic symptoms and 25 with headache; 5 had both local and systemic symptoms. In 2 cases blindness was the presenting complaint. Local signs of inflammation of the temporal arteries frequently postdated the pain by a few days to several weeks. Systemic symptoms have occurred a few weeks or even a few months before the local signs became apparent. Thus prolonged observation may be required in order to ascertain the diagnosis. Once the characteristic changes in the temporal arteries have developed, the diagnosis is obvious and other conditions need not be seriously considered in the clinical differential diagnosis. The duration of the disease has varied from eight weeks to thirty months. The average duration for the reported cases was seven and three-quarters months.

The etiology of temporal arteritis, as of most other forms of arteritis, remains unknown. Horton and his co-workers<sup>1</sup> found actinomyces from culture of the biopsy specimens of the first 2 cases but concluded after study that this was probably a contaminant. MacDonald and Moser<sup>14</sup> found *Staphylococcus aureus*, Bowers<sup>15</sup> found "gram-positive cocci in

14. MacDonald, J. A., and Moser, R. H.: *Ann. Int. Med.* **10**:1721-1726 (May) 1937.

15. Bowers, J. M.: *Arteritis of the Temporal Vessels: Report of a Case*, *Arch. Int. Med.* **66**:384-392 (Aug.) 1940.

16. Dick, G. F., and Freeman, G.: *Temporal Arteritis*, *J.A.M.A.* **114**:645-647 (Feb. 24) 1940.

clusters," and Dick and Freeman<sup>16</sup> found *Streptococcus viridans*. No organism has been found consistently or in a significant number of cases. Cultures of the biopsy specimens of the artery segments have not been taken in most cases. There is no clinical evidence to indicate that allergy is a factor in the etiology and no case in which there was significant eosinophilia in the peripheral blood has been reported. Of the 43 reported cases hypertension was present in 5, coronary heart disease in 4, diabetes in 2, asthma, intermittent claudication, paralysis agitans, eczema of the scalp, and polyneuritis each in 1 case. Oral sepsis has been emphasized in 3 cases, and in most reports the status of the teeth is not mentioned. In Profant's<sup>17</sup> case 1 there was a definite exacerbation of symptoms after extraction of an infected tooth. The disease has occurred in edentulous patients, however, so that the possibility of oral sepsis per se being the etiologic factor seems remote. Distant foci of infection including oral sepsis, with or without bacterial allergy, have been hypothesized as being etiologically significant.<sup>18</sup> As yet the hypothesis is unproved. The fact

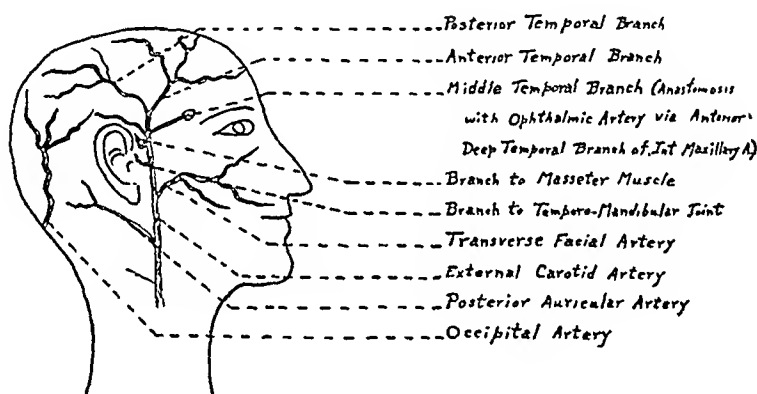


Fig. 15.—Schematic diagram of the temporal artery and its branches.

that this disease occurs apparently only in the older age group, of 55 to 79 years, would suggest that degenerative arterial disease is at least associated with it and perhaps predisposes to it. Trauma to the temporal arteries, predisposed by their superficial location and marked tortuosity, may possibly be a factor in the pathogenesis of the lesion.

Laboratory findings in the disease are quite constant but not diagnostic. There is usually a mild anemia and a mild to moderate leukocytosis with a preponderance of polymorphonuclear leukocytes and some "shift to the left." The sedimentation rate is usually moderately increased and may be extremely rapid.

The inflammatory process in the temporal arteries is the characteristic and dominant feature of the disease. Evidence of arteritis of other branches of the external carotid artery has been stressed by some authors,

17. Profant, H. J.: *Ann. Otol., Rhin. & Laryng.* 53:308-325 (June) 1944.

18. Curtis, H. C.: *Am. J. Med.* 1:437-446 (Oct.) 1946.

notably Kilbourne and Wolff.<sup>19</sup> The clinical symptomatology suggested that other cranial vessels were involved. Careful study of the anatomic distribution of the temporal arteries (fig. 15) shows that this is not necessarily true. The first branch of the temporal artery is the transverse facial artery, which if involved would explain the pain over the face. Two small branches then go to the masseter muscle and the temporomandibular joint, thus explaining the difficult mastication and pain in the jaws and temporomandibular joints. Pain and redness around the eyes and over the forehead and scalp may be accounted for by the involvement of the anterior temporal branches and their tributaries. Similar symptoms over the parietal and occipital regions may be attributed to the posterior branches and their tributaries. Phlebitis probably contributes to local edema for, although it has been denied by most investigators, phlebitis has been found by some<sup>20</sup> and was demonstrated in our case 2. Arteritis of the occipital artery has been assumed by some<sup>21</sup> but never proved. In 1 case<sup>2</sup> biopsy was attempted but diseased vessels could not be demonstrated. The symptomatology suggesting such involvement may have been due to arteritis of the smaller radicles of the posterior temporal branch.

Definite evidence of arteritis in vessels other than the branches of the temporal artery in cases not autopsied is sparse despite general agreement that there must be some generalized arteritis. Lack of pulsation in the dorsalis pedis and posterior tibial arteries has been pointed out but is of a questionable significance in this age group. Dantes<sup>22</sup> noted an area of thickening on the right dorsalis pedis artery in his case. Tenderness was not mentioned and biopsy could not be performed. The question of radial artery involvement was raised in Jennings's<sup>23</sup> case 1, and Scott and Maxwell<sup>24</sup> mentioned tenderness along the course of the arteries of the arm. In case 6 of Cooke and his associates<sup>2</sup> a radial arteritis was actually found at autopsy. The presence of pains in the joints and muscles and generalized pain in the limbs has been offered as evidence of brachial and femoral arteritis, but this has not been confirmed. Residual arthralgia was noted in 1 case.<sup>25</sup> Coronary and mesenteric

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19. Kilbourne, E.D., and Wolff, H. G.: *Ann. Int. Med.* **24**:1-10 (Jan.) 1946.

20. Chasnoff and Vorzimer.<sup>3</sup> Heusner.<sup>6a</sup>

21. (a) Chasnoff and Vorzimer.<sup>3</sup> (b) Bowers.<sup>35</sup> (c) Sprague, P. H., and MacKenzie, W. C.: *Canad. M. A. J.* **43**:562-564 (Dec.) 1940.

22. Dantes, D. A.: *Temporal Arteritis*, *J.A.M.A.* **131**:1265-1269 (Aug. 17) 1946.

23. Jennings, G. H.: *Lancet* **1**:424-428 (Feb. 19) 1938.

24. Scott, T., and Maxwell, E. S.: *Internat. Clin.* **2**:220-223 (June) 1941.

25. Hoyt, L. H.; Perera, G. A., and Kauvar, A. J.: *New England J. Med.* **225**:283-286 (Aug. 21) 1941.

arteritis have been mentioned in the fatal cases; yet in no case has coronary or mesenteric thrombosis been reported in the course of the disease. Increasing angina pectoris was not noted in cases with preexisting angina.

Cerebral arteritis has been hypothesized by Bowers,<sup>15</sup> Chasnoff and Vorzimer<sup>3</sup> and others<sup>26</sup> but is rather difficult to evaluate. The usual symptoms which led to the assumption of cerebral involvement were mental confusion, depression and lassitude which, in the face of anorexia with concomitant deficiencies, dehydration and fever, especially in the age group involved, require extremely careful evaluation. Cooke and his co-workers<sup>2</sup> found a spinal fluid protein of 130 mg. per hundred cubic centimeters in their case 1. In cases 2 and 4 there were significant elevation of protein (70 mg. per hundred centimeters) and in cases 5, 6 and 7 values were normal. In our cases 1 and 3 values were normal for the spinal fluid protein. In cases 3 and 6 of Cooke and his associates,<sup>2</sup> with a high spinal fluid protein in one and with a normal spinal fluid protein in the other, there was definite cerebral arteritis at autopsy. It is also interesting to note that of the 6 patients who died of or during the disease, 4 died of cerebral vascular accidents.

Disease of the retinal vessels in temporal arteritis is common and is the most formidable complication seen in the nonfatal case. Blindness was found in 13 of the 43 previously reported cases and in 3 of our cases, a total incidence of 16 of 48 cases, or 33.3 per cent. In 9 of these cases blindness was bilateral and in 7, unilateral. In a few cases gross perception of light has returned, as in our case 1. Transient amaurosis for a few hours has also been noted and was exemplified in our case 2. This is presumably due to spasm of the retinal vessels. Blindness lasting for a week and subsequently subsiding was found in our case 4. This is unusual, and no good explanation is apparent. Perhaps vasospasm of longer duration led to ischemia and edema of the retina producing blindness until the edema subsided and permitted return of function to those nerve fibers not irreversibly damaged. Other ocular symptoms such as scotomas, aching of the eyes, diplopia, pain on motion and photophobia are of fairly common occurrence. The mechanism of blindness is not well understood. Patients often complain of "spots," blind spots, or quadrantic field defects prior to loss of vision, which is usually described as "a shade being gradually drawn." Careful ophthalmoscopic findings have not been recorded in many cases. There is no proof that the process spreads from the temporal artery along vascular pathways to the artery of the

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26. (a) Scott and Maxwell.<sup>24</sup> (b) Gordon, L. Z., and Thurber, D. C.: Temporal Arteritis: Report of a Case and Comparison with Respect to Periarteritis Nodosa, *Arch. Path.* 42:402-411. (Oct.) 1946. (c) Post, L. T., and Sanders, T. E.: *Tr. Am. Ophth. Soc.* 41:241-250, 1943. (d) Curtis.<sup>18</sup>

retina. A possible pathway for such extension from the temporal to the retinal vessels has been pointed out by Johnson, Harley, and Horton,<sup>27</sup> who state that "the anterior deep temporal arteries have an anastomosis with the lacrimal branch of the ophthalmic artery" which gives off the central artery of the retina as well as the anterior and posterior branches to the optic nerve. The anterior deep temporal artery is usually a branch of the internal maxillary artery. The former does have a large anastomosis with the middle temporal branch of the temporal artery so that the pathway is complete though extremely indirect. Thus far no case of blindness in either eye has been reported without arteritis of the corresponding temporal artery. Longitudinal extension along the pathway mentioned from the temporal to the retinal arteries has not been demonstrated but this method of spread elsewhere has been suggested by post-mortem findings.<sup>2</sup> Since blindness is usually a late manifestation of the disease, section of the middle temporal branch of the temporal artery early in the course of the disease might conceivably be of some prophylactic value against the development of blindness.

Wagener<sup>28</sup> has reviewed carefully and comprehensively the subject of blindness in temporal arteritis. He classifies the lesions into three groups: closures or thromboses of the central artery of the retina or of branch arterioles, ischemic optic neuritis and an indeterminate group. He also reviews the cases with blindness thus far described, classifies them and describes the ophthalmoscopic findings in each. All blindness in this disease must be attributed in the final analysis to retinal or optic nerve ischemia secondary to arteritis. The only histologic ocular findings which are available are those of case 6 of Cooke and associates,<sup>2</sup> who found that the "optic nerves showed marked softening" and "the lumen (of both retinal arteries) was obliterated by cellular fibrous tissue obviously formed during the organization of a thrombus" (see Cooke and associates,<sup>2</sup> fig. 7). No treatment or prophylactic measures for the blindness have been offered. Johnson, Harley and Horton<sup>27</sup> believe vasodilator drugs to be ineffective and even harmful. Our first patient became blind in spite of treatment with amyl nitrate and nicotine acid.

An evaluation of temporal arteritis as a possible pathologic entity must include the distribution of the lesions as well as the histologic variations. There are relatively few histologic lesions which are pathognomonic of a single disease process. The tissues of the body are capable of reacting to noxious stimuli in a limited number of ways. The arteries and veins are no exception to this rule. Similar histologic patterns may be produced by a wide variety of stimuli. Conversely, a variety of patterns may be

27. Johnson, R. H.; Harley, R. D., and Horton, B. T.: *Am. J. Ophth.* **26**:147-151 (Feb.) 1943.

28. Wagener, H. P.: *Am. J. M. Sc.* **212**:225-228 (Aug.) 1946.

produced by apparently identical stimuli in different persons under different circumstances. There are apt to be considerable variations in the

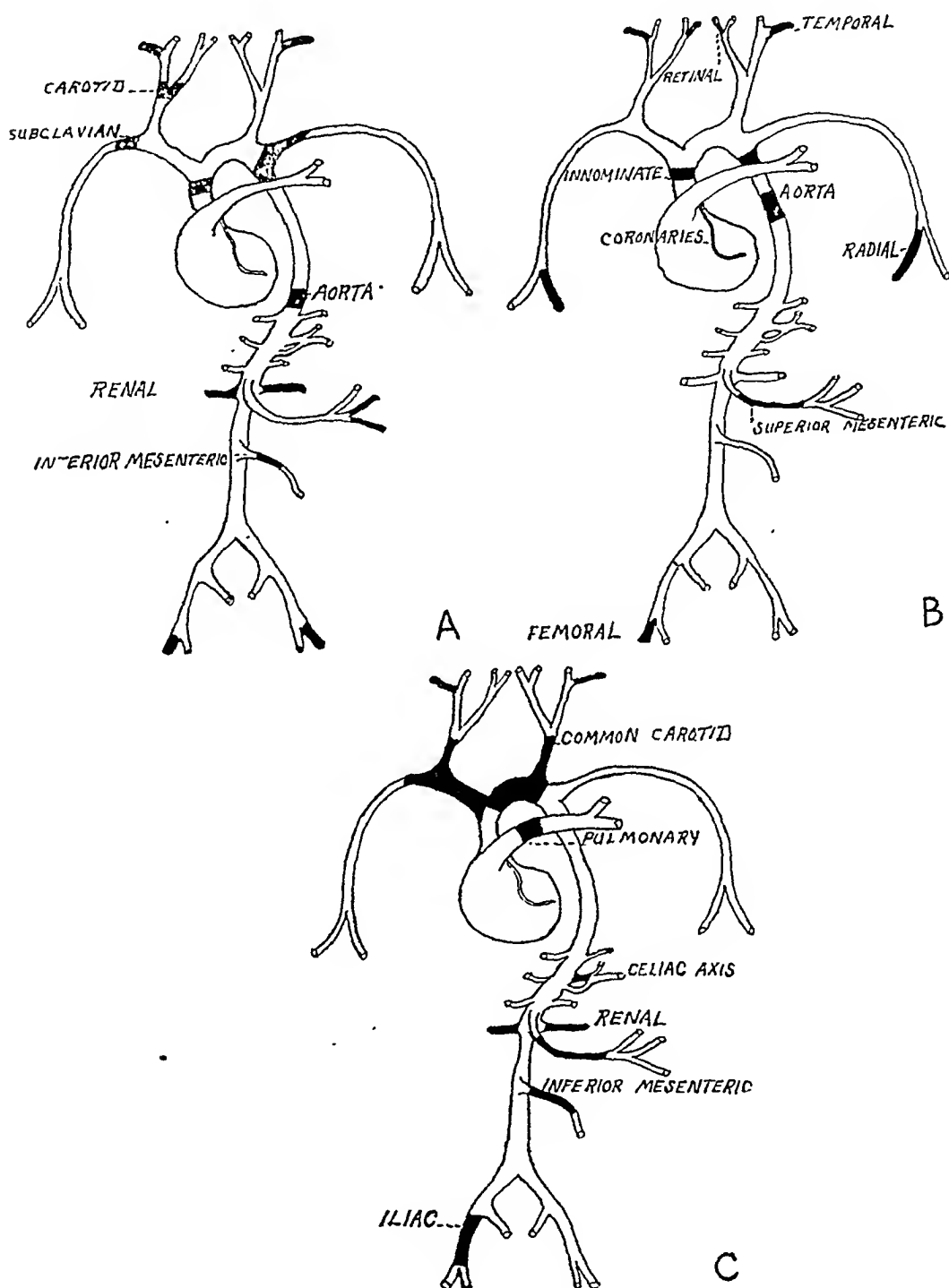


Fig. 16.—The distribution of the arteritis in autopsied cases: *A*, Cooke and others, case 3; *B*, Cooke and others, case 6; *C*, Sproul's case.

response to a single etiologic agent in the acute, subacute, chronic and healed phases of a disease process. The histologic appearance at any

specific time is dependent not only on the character, virulence, concentration, duration of action and site of action of the noxious agent but also on the resistance of the host and the reaction capacity of the particular organ affected. Any attempt, therefore, to correlate histologic pathology with the disease process necessitates the integration of the local lesion and the distribution of such lesions with the general effect on the host and should include the general clinical picture.

In 28 of the 48 reported cases of temporal arteritis the only demonstrable vascular lesions were in one or both of the superficial temporal arteries. Second in frequency of involvement is the central artery of the retina which has always been accompanied by temporal arterial disease on the same side. In relatively few cases have other vessels been studied histologically. There are, however, certain observations which show that this vascular disease is not limited to the temporal arteries and their branches. In the 4 patients who have been examined at the autopsy table vascular lesions similar to those examined in biopsy specimens of the temporal arteries have been found in other vessels of the body (fig. 16). The group of cases reported by Cooke and associates<sup>2</sup> form an important link in the development of our appreciation of this process as a potential widespread vascular disease. Their 7 patients ranging in age from 66 to 73 years all showed inflammatory lesions of the temporal artery. Confirmatory biopsies were performed in 6 of the 7 cases. In 6 cases there were symptoms suggesting a generalized arterial disease. In 2 of these patients this was confirmed by postmortem examination. A characteristic histologic picture was noted in the aorta, temporal, radial, subclavian, femoral, coronary, renal, retinal and mesenteric arteries (fig. 16 A, B). In the case reported by Sproul<sup>29</sup> there was involvement of the temporal, carotid, innominate, subclavian, pulmonary, celiac, mesenteric, renal and iliac arteries as well as involvement of the aorta (fig. 16 C). In the case reported by Chasnoff and Vorzimer<sup>3</sup> autopsy was said to have revealed changes in other vessels similar to those which had been previously seen in the temporal arteries. The distribution of these lesions has not yet been published.

Although the etiologic agent responsible for temporal arteritis has not yet been demonstrated, the vascular lesions are sufficiently uniform to substantiate the clinical concept that this disease stands apart from other known vascular diseases. In temporal arteritis there is a granulomatous type of reaction involving all coats of the artery, usually greatest in the media. Areas of necrosis are accompanied by a diffuse infiltration of lymphocytes, plasma cells, occasional eosinophils and occasional polymorphonuclear leukocytes. The mononuclear cells seem to predominate

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29. Sproul, E. E.: *New York State J. Med.* 42:345-346 (Feb. 15) 1942.

in the cellular infiltrate. Multinuclear giant cells are conspicuous components of the lesion (fig. 2) although they are vastly outnumbered by the mononuclear cells. The necrosis of the media appears to develop in small foci. Massive necrosis of the media has not been observed. The lesion apparently extends rather slowly and the host is usually able to repair the damaged tissue as the process extends along the vessel. Granulation tissue is formed and is eventually replaced by scar tissue. The cellular reaction apparently depends on the stage of the process. Although many types of inflammatory cells are found it appears significant that mononuclear cells predominate in the picture. Multinucleated giant cells appear to be formed from the proliferating endothelial cells lining the newly formed capillaries. The internal elastic lamina seems to act as a buffer but as an incompletely effective barrier to involvement of the intima. As the process extends through the internal elastic lamina the intima becomes vascularized and fibroblastic proliferation appears stimulated.

With further extension of the inflammatory process into the intima there may be destruction of the endothelial lining and the development of thrombi with obliteration of the lumen. The inflammatory process extending through the periadventitial tissues surrounds but does not appear to penetrate the periarterial nerves. Compression of these nerves by inflammatory tissue may contribute to the excruciating pain of which these patients complain.

It is difficult to evaluate the role of the vasa vasorum in this process. The granulomatous nodules are, for the most part, found in the distribution of the vasa vasorum, i. e. in the media and adventitia. Many of these nutrient vessels reveal striking changes. Some of them show an inflammatory infiltration of their walls, but no fibrinoid necrosis is seen. Some of them have thickened hyalinized walls suggesting a lesion that is of longer duration than that of the surrounding inflammatory reaction. It is possible that the disease process arises in and spreads by way of these nutrient vessels. It is to be noted, however, that the vasa vasorum in close proximity to one another are not uniformly affected but show considerable variation in histologic appearance.

Phlebitis has rarely been mentioned as a complication of temporal arteritis. In 2 of the cases reported by Horton and Magath<sup>4</sup> there was evidence of phlebitis in one of the retinal veins with the development of hemorrhage and exudates. In case 3 of Cooke and associates<sup>2</sup> there was involvement of the femoral vein with fibrosis and recanalization. No other reports of venous involvement in temporal arteritis have been found. In fact, the absence of phlebitis has been mentioned<sup>19</sup> as one of the points of differentiation between this process and that found in thromboangiitis obliterans. The phlebitis which has been observed in the venae



comites of the temporal artery appears to be a secondary lesion spread by direct extension of the periarterial granulomatous process. The portion of the vein adjacent to the artery may be severely involved while its opposite wall remains intact (figs. 1 and 9). The severe and extensive involvement of the periadventitial tissues leads us to believe that phlebitis will be demonstrated more frequently if the accompanying veins are carefully examined.

It is surprising that no previous reports of temporal arteritis have shown the production of aneurysms. A process which destroys the media with multiple areas of necrosis might be expected to facilitate the development of such a process. The rarity of its occurrence may be due to the marked desmoplastic reaction in the granulomatous tissue, to the tendency for the destructive process to be limited by the internal elastic lamina or to the strengthening of the arterial wall by the collagenous intimal thickening.

Although temporal arteritis appears in an age group in which we expect to find arteriosclerosis, there is nothing in the lesions in most cases of temporal arteritis to suggest that the degenerative lesions of atherosclerosis play a part. In cases 3 and 6 of Cooke and associates<sup>2</sup> arteritis seemed more intense in the region of the atheromatous plaques. They state that in some areas "there seemed to be a combination of atheroma and arteritis." That atherosclerotic lesions have been demonstrated in other vessels in those patients is only to be expected.

There is little to suggest any relationship to tuberculous, syphilitic or rheumatic arteritis. No tubercles, gummas or Aschoff bodies have been associated with the lesions of temporal arteritis. None of the patients have shown positive serologic reactions for syphilis. In none of the cases has there been any evidence of active tuberculosis. The age group, the size of the involved vessels and the paucity of inflammatory lesions in the intima serve to separate the lesions of temporal arteritis from those of rheumatic arteritis.

In thromboangiitis obliterans the large vessels of the lower extremities of young or middle-aged adults are involved by a diffuse panarteritis and phlebitis. In some respects the process is similar to that seen in temporal arteritis. It appears to start in the adventitia and progress through the media to the intima. The steadily progressive process results in thrombosis and obliteration of the arteries and veins with eventual obliteration of the blood supply to the affected part. Giant cells are frequently seen in the granulomatous reaction in the media.

In the acute nonsuppurative arteritis occasionally seen in typhoid fever, scarlet fever, diphtheria and pneumonia the process appears to arise in the intima and is frequently followed by thrombosis. There is usually a subintimal connective tissue proliferation accompanied by an

exudate of mononuclear cells which may extend throughout the vessel wall. Similar lesions may be found in typhus fever, Rocky Mountain spotted fever, disseminated lupus erythematosus, dermatomyositis and in reactions to the sulfonamide compounds. These lesions, however, are usually widespread and are commonly found in the arterioles, smaller arteries and venules. They are characterized by a fibrinoid type of necrosis in which fibrin-like material is deposited in the wall of the vessel. There is usually a perivascular lymphocytic infiltration about the arterioles and venules.

In periarteritis nodosa there is predilection for the muscular type of medium and small size arteries which supply the viscera. This process appears to originate in the adventitia and spreads throughout the wall, producing areas of necrosis in the media. Aneurysms are commonly produced. Thrombosis, rupture and hemorrhage are frequently seen. The cellular exudate depends on the duration of the process. Although polymorphonuclear leukocytes and eosinophils frequently predominate, these cells may be replaced later by plasma cells and lymphocytes. Giant cells are sometimes reported but usually do not form a conspicuous part of the picture. The process tends to be rapidly progressive, and most cases end fatally within a year or two.

The panarteritis seen in extremities subjected to rapid vibration by such instruments as the pneumatic drill is different from that seen in temporal arteritis. In the former there is an extensive infiltration of all coats of the vessel with thrombosis and sometimes recanalization. Recent studies showing the production of arterial lesions by the injection of foreign proteins<sup>30</sup> suggests that a nonspecific arteritis with many of the histologic characteristics of temporal arteritis may be produced experimentally.

Although certain similarities are noted in the histologic structure of the pathologic process of temporal arteritis and in that of other non-suppurative inflammatory diseases of the arteries, the total picture is sufficiently different to warrant separate classification of this disease process. In some patients many vessels may be involved, but the symptomatology is largely an expression of the involvement of the temporal arteries and sometimes of the retinal arteries. The pathologic process, although not pathognomonic of this disease, is usually distinctive.

Although temporal arteritis is not entirely benign, as Horton, Magath, and Brown<sup>1</sup> originally believed, its relative benignity is borne out by review of the cases thus far reported. In the 43 reported cases plus our 5 cases only seven deaths occurred, one of which we exclude from the disease mortality. This case was first described by MacDonald and

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30. Hawn, C.: Personal communication to the authors.

Moser<sup>14</sup> and later by Post and Sanders.<sup>26c</sup> The patient lived six years after the disease had apparently subsided and died of a cerebral vascular accident. In 1 of Horton and Magath's cases<sup>4</sup> and in Jennings's case 2<sup>23</sup> the patient died of unrelated causes some time after the temporal arteritis had subsided.

Sproul's<sup>29</sup> patient died of congestive heart failure and pneumonia eight weeks after the onset of his disease. He also had diabetes mellitus and coronary heart disease but, since there was evidence of generalized arteritis, this case has been included as a fatality. Chasnoff and Vorzimer's<sup>3</sup> patient died fourteen months after the onset and three months after the apparent subsidence of temporal arteritis. Postmortem examination showed generalized arteritis, and this case has been included in computing the disease mortality. Among the cases of Cooke and his co-workers<sup>2</sup>, cases 3 and 6 showed definite generalized arteritis. In case 2 the patient died shortly after the onset of the disease, and permission for necropsy was not obtained. It was assumed that he died of the disease. These 3 cases are included in computing the disease mortality. Similarly Curtis'<sup>18</sup> patient died three and one half months after the onset of the disease with generalized arteritis and is included as a fatality. This makes a total of six deaths attributed to the disease in 48 cases, or a disease mortality of 12.5 per cent. In comparison with other forms of generalized arteritis this is a very low mortality. Compared with systemic diseases in general in this age group, the process is relatively benign. The fact that it is not entirely benign should, however, be recognized.

All methods of treatment to date have been ineffective with the exception of section of the temporal arteries. The therapeutic measures which have been tried are: administration of salicylates, and of liver by mouth and injection, potassium and sodium iodide, arsenic, mercury, "prontosil" (azosulfamide), sulfanilamide, sulfathiazole, vitamins A, B complex, and D, acetophenetidin, cobra venom, amyl nitrite and nicotinic acid, and finally section of the temporal vessels. In 1 case<sup>31</sup> the Sanders oscillating bed was used with apparent improvement in that case. Biopsy was first utilized for diagnostic purposes but was found useful for therapy. Section of the temporal arteries may be done easily under local anesthesia. Two or 3 cm. of the artery should be resected between ligatures together with the vein and the perivascular sympathetic nerve fibers close to the origin of the artery but above the branches to the masseter muscle and the temporomandibular joint (fig. 15). This is also above the site of origin of the transverse facial artery and the middle temporal artery. It

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31. Schaefer, C. L., and Sanders, C. E.: *Am. Heart J.* 24:410-411 (Sept.) 1942.

corresponds to the area of skin just anterior to the superior margin of the pinna of the ear. Interruption of the perivascular sympathetic nerve fibers has been given as the reason for relief of local symptoms. In most cases relief of headache, local pain and tenderness has been obtained after section of the affected vessels. At times it is dramatic, as it was in our case 2. The systemic symptoms are not relieved by this procedure, however, and they usually persist for what would presumably correspond to the natural course of the disease.

The homogeneity of the cases thus far reported warrants classification of temporal arteritis as a distinct disease entity. Horton, Magath, and Brown<sup>1</sup> chose to await observation of more cases before the "condition is dignified by nomenclature." The question has been raised, notably by Dantes<sup>22</sup>, Cooke and associates<sup>2</sup> and Kilbourne and Wolff,<sup>10</sup> whether or not "temporal arteritis" is too restrictive a term for a disease characterized by such obvious and definite systemic manifestations. Kilbourne and Wolff<sup>10</sup> suggested the term "cranial arteritis," which would, however, be open to the same criticisms as "temporal arteritis." Whether a name indicative of the systemic nature of the disease should be adopted at this time is also open to question. The nomenclature of diffuse vascular inflammatory diseases, especially of the lupus erythematosus disseminata, dermatomyositis, periarteritis nodosa group or generalized "vascularitis" is already inadequate. While it is true that temporal arteritis probably represents a much more widespread vascular disease than the name indicates, the inflammation of the temporal arteries has thus far remained the constant and dominant feature of the disease. Until etiologic classification is possible retention of the simple descriptive term "temporal arteritis" is suggested.

#### SUMMARY AND CONCLUSIONS

Two cases of temporal arteritis are presented in detail. Three additional cases are briefly reported. The essential data of all the previously reported cases are presented and analyzed.

The pathologic changes in biopsy specimens of artery segments of 1 of our cases are described in detail. A dissecting aneurysm of one temporal artery and phlebitis of the accompanying veins were found. The pathology of the disease in general is discussed.

From the analysis and study of the clinical and pathologic data of all the reported cases certain facts are apparent.

- (a) Temporal arteritis is a distinct clinical entity affecting people of the older age group and characterized by local symptoms consisting of painful, tender, red, swollen, nodular and thrombosed temporal arteries with edema and pain in the adjacent structures and systemic symptoms consisting of fever, malaise, anor-

exia, loss of weight and weakness. The edema of the overlying skin is probably contributed to by phlebitis of the accompanying vein.

- (b) Blindness is relatively common in this disease and was found in one or both eyes in 33.3 per cent of the cases. The possible prophylactic value of section of the middle temporal artery early in the disease is suggested.
- (c) The local symptoms can be reasonably explained on the basis of inflammation of the temporal vessels and their branches.
- (d) The systemic symptoms probably indicate a more generalized arteritis.
- (e) The mortality of this disease, 12.5 per cent, is considerably less than that of most other forms of arteritis.
- (f) The cause of the disease is unknown.
- (g) Since the involvement of the temporal vessels and the symptomatology arising from it are constant and dominant features of the disease, it is suggested that the term "temporal arteritis" be retained until etiologic classification is possible.

## THROMBOSIS OF THE INFERIOR VENA CAVA DUE TO HYPERNEPHROMA

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THE CASE herein described is reported because of three cardinal points: first, the relative frequency with which dilated abdominal veins due to cirrhosis of the liver were mistaken for those due to obstruction of the inferior vena cava; secondly, the unusual venous thrombosis that extended from the femoral veins through the inferior vena cava to the right auricle of the heart, and lastly, because increased awareness of this condition may lead to its more frequent diagnosis.

### REPORT OF A CASE

The patient was a 70 year old white man, first admitted to a hospital on Aug. 27, 1946, with edema of the legs for three weeks. He also had noted occasional pain in the left upper abdominal quadrant for several months. He had had gonorrhea about forty-five years previously and admitted having been a heavy beer drinker until twenty years ago. There were no other pertinent facts disclosed at this time.

Physical examination revealed the following symptoms: There were a few crepitant rales at the base of the left lung. The heart was somewhat enlarged to the left, and the blood pressure was 152 mm. of mercury systolic and 78 mm. of mercury diastolic. Occasional extrasystoles were noted. The liver was palpated 5 fingerbreadths below the right costal margin and was somewhat tender. The tip of a mass thought to be spleen was palpated below the left costal margin. There was a well developed collateral circulation over the abdomen, more pronounced along the flanks than around the umbilicus. Edema of the ankles (2+) was present.

The diagnosis at that time was arteriosclerotic heart disease and possible cirrhosis of the liver.

The patient was placed on a cardiac regimen of digitalis and diuretics, after which the rales in the lungs rapidly disappeared. Edema of the ankles persisted. The cephalin flocculation, alkaline and acid phosphatase contents, phosphorus level and blood were normal at this time. Total plasma protein was 6.4 Gm. per hundred cubic centimeters. The veins of the abdominal wall were noted to fill from below. Despite therapy, the liver did not decrease in size. An electrocardiogram was interpreted as indicative of "myocardial damage." A punch biopsy of material from the liver was reported to reveal "congestion of the liver." The urine was normal.

Two weeks later the patient signed his release from the hospital. The diagnosis on discharge was "cirrhosis of the liver." Four days later, on Oct. 8, 1946, he was admitted to Kings County Hospital. His complaints were considerable dyspnea and weakness. At this time he gave a history of having had dyspnea and pedal edema

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for three months. He also had noted a dull, inconstant pain in the left upper and left lower abdominal quadrants. The pain was not related to meals or to defecation. He again gave a history of fairly heavy alcoholism.

Physical examination revealed an emaciated, dyspneic, rather anemic man 70 years of age who had evident weakness. There was slight distention of the veins of the neck. Moist rales were present at the base of the right lung. The heart tones were regular but of poor quality. No murmurs were present. The blood pressure was 150 mm. of mercury systolic and 84 mm. of mercury diastolic. A firm edge of liver was felt 4 fingerbreadths below the right costal margin. A mass thought to be spleen was palpated in the upper abdominal quadrant 4 to 5 fingerbreadths below the left costal margin. The abdominal veins were distended and were most prominent along the lateral region of the abdominal wall and the flanks. These veins filled rapidly from below. No caput medusae was present. There was edema (2+) of the legs and feet. Rectal examination did not reveal any hemorrhoids or masses.

The diagnosis was hepatosplenomegaly, probably due to hepatic cirrhosis, and arteriosclerotic heart disease.

*Laboratory Studies.*—The urinalysis disclosed a specific gravity of 1.018, a trace of albumin and a few casts and white blood cells per high power field. The hemoglobin content was 8 Gm. per hundred cubic centimeters as determined by the Sahli method. The peripheral blood count revealed 4,300,000 red blood cells per cubic millimeter; the white blood cells numbered 14,200, with 70 per cent neutrophilic polymorphonuclear cells, 25 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophilic polymorphonuclear cells. The circulation time (arm to tongue with triketocholanic acid) was fourteen seconds (normal range, eight to sixteen seconds). The reaction to a Wassermann test of the blood was negative. At this time the blood urea was 42 mg. and the fasting blood sugar 88 mg. per hundred cubic centimeters and the alkaline phosphatase 5.6 units (normal range, 2 to 8 units). The reaction to the cephalin flocculation test was negative on two occasions. The total blood cholesterol level was 200 mg. per hundred cubic centimeters, with 125 mg. as cholesterol esters and 75 mg. as free cholesterol.

During the following month the value for the total cholesterol esters was 126 mg. per hundred cubic centimeters, with 67 mg. of cholesterol esters and 59 mg. of free cholesterol. The total plasma protein was 5.8 Gm. per hundred cubic centimeters, with 3.4 Gm. of albumin and 2.4 Gm. of globulin. One week later the total plasma protein was 6.2 Gm. per hundred cubic centimeters, with 3.8 Gm. of albumin and 2.4 Gm. of globulin. The icteric index was 4. The blood phosphorus level was 4 mg. per hundred cubic centimeters.

An electrocardiogram showed depression of the S-T segments in leads II and III, consistent with digitalis effect and myocardial damage.

A roentgenogram of the chest revealed an irregular nodule in the left mid-pulmonary field, which was interpreted as a possible metastatic lesion. The osseous system, including the extremities, spine, skull and pelvis, was free from metastasis. A roentgenogram made after barium enema showed no obstruction or intrinsic lesion in the colon. A roentgenogram of the esophagus did not reveal esophageal varices.

*Course in the Hospital.*—On October 15 the patient first noted dark-colored urine. He complained of frequency and dysuria. Careful questioning disclosed that he had had a similar attack of hematuria for a short period about one year ago. The urine gave a positive reaction to the benzidine test and contained albumin (1 plus) and numerous casts, red blood cells and white blood cells.

Three days later a cystoscopy was performed. The prostatic urethra was elongated. There was protrusion of the lateral lobes (1 plus) and a median bar (2 plus). The mucosa of the bladder showed trabeculation (1 plus).

In view of the gross hematuria and of the cystoscopic findings, the mass in the left upper quadrant noted on the previous examination was reevaluated at this time. It was now thought to be the left kidney rather than the spleen. Perirenal air studies confirmed this impression (fig. 1).

On October 24 an intravenous pyelogram was made and two days later a retrograde pyelogram.



Fig. 1.—Perirenal air study showing large tumor of the left kidney.

On cystoscopy, the left ureteral orifice was somewhat inflamed. A no. 4 catheter passed easily up the right ureter for a distance of 25 cm. On the left side an obstruction was encountered 2 cm. from the ureteral orifice. Phenolsulphonphthalein dye appeared on the right side after five minutes, while on the left there was none apparent after ten minutes.

Retrograde pyelography revealed that there was enlargement of the left kidney and tortuosity of both ureters, particularly the left. There was no irregularity or dilatation of the calices or pelvis of the right kidney. However, the left kidney showed poor filling, with a persistent filling defect in the pelvis and in the upper 3



cm. of the ureter. The conclusion was that the patient had (1) bilateral ptosis of the kidneys and (2) a space-occupying lesion of the left kidney, the pelvis and the upper part of the left ureter, possibly on the basis of a papillary intrapelvic growth (fig. 2).

The hematuria gradually subsided. However, frequency and some dysuria persisted. The urine repeatedly contained a trace of albumin (1 plus) and variable numbers of red and white blood cells. The enlargement of the collateral veins became more prominent on the back as well as on the lateral part of the abdomen and chest.

Studies of the blood were undertaken to discover if there was any systemic bleeding tendency. The blood coagulation time by test tube method was five



Fig. 2.—Intravenous urogram. The left kidney shows enlargement and poor filling, with persistent filling defect within the pelvis and the upper 3 cm. of the ureter.

minutes, the bleeding time thirty seconds and the clot retraction time normal. The platelets numbered 140,000 per cubic millimeter. The prothrombin time was fifteen seconds, with a control of fourteen seconds. A Rumpel-Leed cuff test elicited a strongly positive reaction. The white blood cells numbered 11,200 per cubic millimeter, with a normal differential count. The hemoglobin content was 6 Gm. per hundred cubic centimeters as determined by the Sahli method. Two blood cultures were sterile. The findings pointed to an increased capillary fragility. A transfusion of 500 cc. of blood was given.

On November 1 a femoral venipuncture for pressure readings was attempted bilaterally but was unsuccessful. The venous pressure in one of the dilated abdominal

veins, namely, the right inferior superficial epigastric vein, was taken. At a point 1 inch (2.5 cm.) above the inguinal ligament the venous pressure was 13 cm. of water. The circulation time from this vein to the tongue, determined with the use of triketocholanic acid, was 14.5 seconds, demonstrating a fairly efficient collateral circulation.

It was thought at this time, in view of the persistent edema of the lower extremities, the pronounced collateral circulation over the abdomen, flanks, back and chest and the presence of a large renal mass with hematuria, that the entire picture

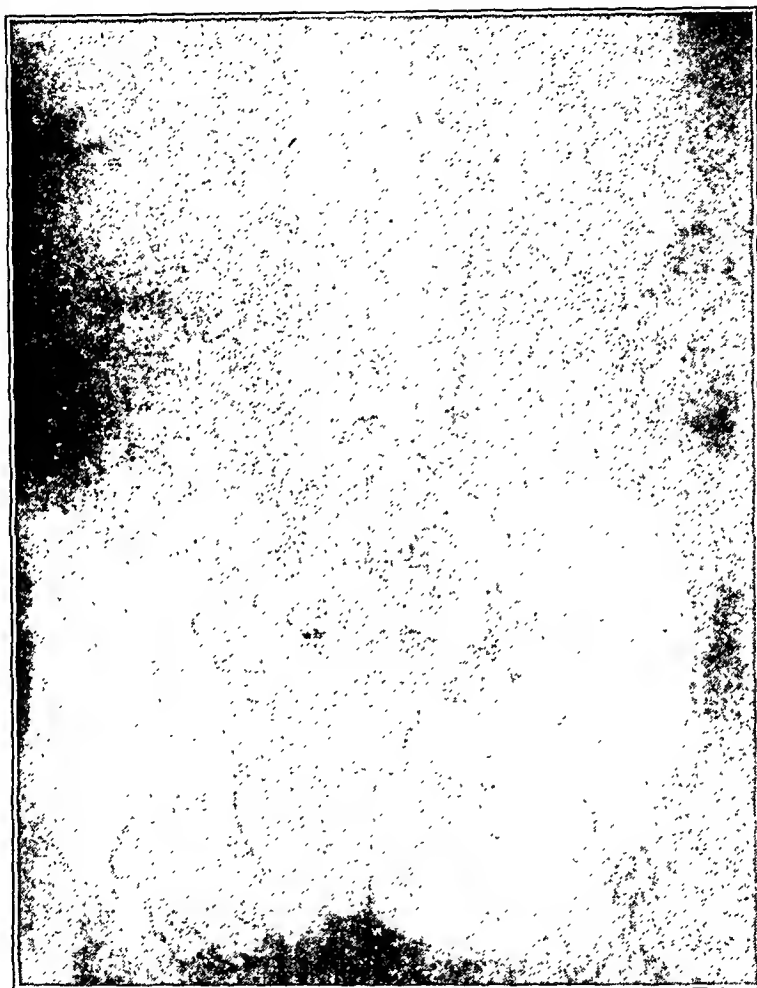


Fig. 3.—Venogram showing block of the femoral vein and the dilated collateral abdominal veins. A wooden ruler was compressed over the abdomen to prevent the "diodrast" from flowing into the collateral abdominal veins and to encourage the flow through the deep veins. Despite this compression, the dye did not enter the femoral vein.

could be explained by the presence of a hypernephroma of the left kidney growing into the left renal vein and the inferior vena cava, with obstruction down to the femoral veins.

Because of the age, the general poor condition of the patient and the probable involvement of the right renal vein, operative intervention was decided against.

During the next week, the edema over the lower extremities continued to increase. The abdomen appeared slightly distended, and the patient complained of vague abdominal pains. Repetition of the studies of the blood revealed the following: The bleeding time was one minute and the coagulation time determined by capillary

tube method was four minutes. The hemoglobin content was 9.5 Gm. per hundred cubic centimeters by the Sahli method, the red blood cell count was 4,100,000 per cubic millimeter and the white blood cells number 8,500 per cubic millimeter, with a normal differential cell count. The prothrombin time was thirteen seconds, with a control of thirteen seconds. The reaction to the Rumpel-Leed cuff test was now normal.

During the next two weeks, the edema of the legs decreased somewhat but persisted enough to obscure most of the veins.

Venipuncture of the femoral veins was again unsuccessful on November 26. The impression that both veins were thrombosed was strengthened.

A week later it was noted that the edema of the lower extremities had decreased still more but that the abdominal collateral circulation was now more prominent. No caput medusae was present.

On December 5, 20 cc. of 70 per cent "diodrast" was successfully injected into the left saphenous vein while roentgenograms were taken simultaneously. The phlebogram thus obtained revealed that the contrast medium did not enter the femoral vein but coursed directly into the superficial circumflex iliac, superficial epigastric, and lateral femoral cutaneous veins to anastomose with the dilated abdominal veins despite pressure applied over the latter. This finally confirmed the clinical impression of thrombosis of the femoral vein (fig. 3).

The patient continued to go gradually downhill. Gross hematuria periodically manifested itself. On Dec. 12, 1946, he died.

*Abstract of Autopsy Protocol.*—The body was that of a poorly developed, extremely emaciated 70 year old white man measuring 64 inches (162 cm.) in length and weighing approximately 80 pounds (36 Kg.). Along the lateral walls of the chest and over the flanks there were distended veins of a mean diameter of about 4 mm. The veins of the neck were not distended. The abdomen was flat; in the left upper quadrant a firm irregular mass was palpable.

The right lung weighed 400 Gm. and the left lung 350 Gm. A firm yellowish white nodule 1.5 cm. in diameter was present in the anterior portion of the upper lobe of the left lung. No other metastasis was noted in either lung.

About 1 cm. below the origin of the right pulmonary artery the lumen of the vessel branch to the right lower lobe was dilated and occluded by an adherent yellow-gray firm thrombus. Hilar and tracheobronchial lymph nodes were small and anthracotic.

The heart was opened while still attached to the arterial and venous trunks (fig. 4). The right auricle contained the terminal portion of a tumor thrombus which extended into it from the inferior vena cava. The left ventricle was somewhat dilated and its wall thickened. The coronary vessels were moderately sclerotic but patent throughout their course.

The right kidney was normal in shape and consistency. It appeared somewhat larger than usual, measuring 11 by 7 by 7 cm. The left kidney was the site of a firm and, for the most part, discrete large tumor mass which measured 19 by 19 by 10 cm. It was embedded in a rather large amount of adrenal fat, which was readily separated from the surrounding tissue. The renal veins were markedly distended and filled by yellowish gray soft tumor tissue. The caliber of the veins reached 2 cm. Section through the mass revealed that almost the entire upper pole of the kidney was replaced by a yellow hemorrhagic soft tumor. The pelvis of the kidney was dilated, displaced downward and partially occupied by the mass. The mucosa was deep red and spongy; protruding into the ureter was a polypoid, rubbery, yellow-gray tumor cast of the pelvis. The ureter was slightly dilated throughout

its course and of a maximum diameter of 0.5 cm. In addition to the renal vein, the suprarenal and inferior phrenic veins were packed with tumor tissue. The inferior vena cava was solidly filled with a tumor resembling a long sausage beginning at the level of the renal vein and extending into the right auricle. However, the tumor did not invade the hepatic veins, which emptied into a channel between the thrombus and the wall of the inferior vena cava. The portion of the vena cava

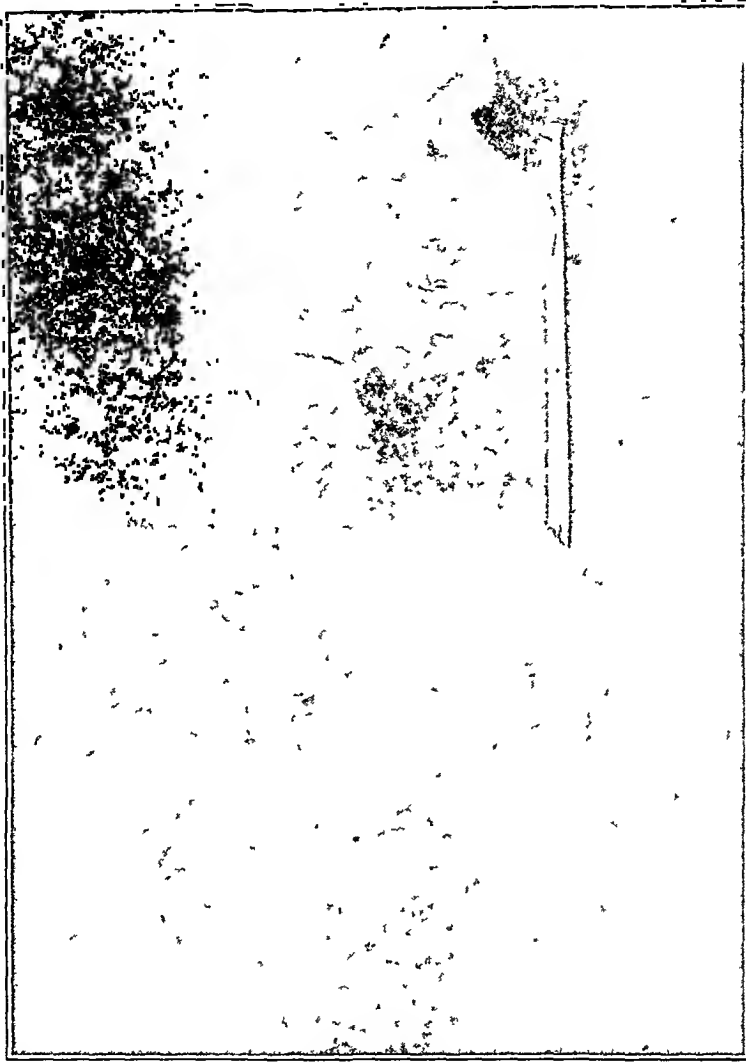


Fig. 4.—Autopsy specimen shows both kidneys sectioned. The tumor of the left kidney is on the right side. The inferior vena cava and the heart are above. The iliac veins are thrombosed below. This shows the tumor thrombus distending the lumen of the inferior vena cava and extending upward into the right auricle of the heart.

and its tributaries below the renal vein, including the left spermatic vein, was totally occluded by a reddish gray organized thrombus.

The fatty tissue surrounding both kidneys contained numerous dilated thin-walled blood vessels, indicative of collateral circulation emptying into the retroperitoneal venous plexus.

The urinary bladder was thick walled and contracted. The surface of the mucosa was hyperemic and partly hemorrhagic, and it contained yellowish gray purulent material. The openings of the ureters were small. The right ureter was normal in caliber throughout. The left ureter was dilated. The prostate was moderately

enlarged; numerous small concretions were present. There were some thromboses in the prostatic plexus.

The spleen was normally firm. There appeared to be an increase in the fibrous tissue. One calcific nodule 2 mm. in diameter was present at the upper pole. The splenic vein was slightly dilated.

The liver weighed 1,400 Gm. It was firm and deep brownish. Cut surfaces showed a nutmeg appearance. Scattered throughout the liver were nine discrete ovoid whitish yellow metastatic nodules of a maximum diameter of 1 cm. The hepatic veins were wide and free of tumor or thrombi.

The right adrenal was small. The medulla was thick and well preserved, with mottled light grayish areas in the central portion. The left adrenal was situated on top of the main tumor mass. Its surface presented the same appearance as that of the right.

The remaining gross findings were compatible with the age of the patient.

*Microscopic Examination.*—There was slight fibrosis of the myocardium and minimal fibrous thickening of the endocardium. The metastasis seen in the lungs in the gross examination was confirmed. The spleen had fibrous thickening of the capsule, which was diffusely infiltrated with small round cells. The pulp was congested. The calcific nodule noted grossly contained amorphous pink-blue material surrounded by a fibrous wall. The liver showed chronic passive congestion; the central veins and sinusoids were congested, with atrophy of hepatic cells.

The nodules seen grossly consisted of metastatic cells. In the adrenals numerous small discrete cortical adenomas and cortical hyperplasia were present. Within the medullary portion were tumor cells. Section of the right kidney revealed moderate congestion, with several small wedge-shaped subcapsular areas of fibrous and round cell infiltration. An occasional glomerulus was hyalinized. There was slight hyaline thickening of the intima of the blood vessels.

Section through the left kidney in the region of the tumor revealed considerable compression and congestion of the parenchyma, with some round cell infiltration. The tumor tissue was arranged in large lobules separated by a fairly thick irregular layer of fibrous tissue. The tumor tissue was seen distending the large blood vessels. The tumor cells were large and for the most part clear, but many had eosinophilic cytoplasm and were arranged in irregular cords, with a suggestion of papillation. The nuclei were large, pleomorphic and hyperchromatic, with occasional atypical mitotic figures and bizarre forms.

The mucosa of the bladder was congested and in part desquamated. There was diffuse round cell infiltration. The prostate contained numerous laminated eosinophilic and basophilic cells. Round or oval masses were present in the acini. There was some glandular and stromal hyperplasia. Many acini were distended with exudate consisting of polymorphonuclear leukocytes, with some infiltration of adjacent tissues. There was moderate squamous metaplasia. The seminal vesicles were normal. Organized canalized thrombi were seen in some of the blood vessels.

*Anatomic Diagnosis.*—The anatomic diagnosis was adenocarcinoma of the left kidney (hypernephroma), with metastasis to the liver, lungs and adrenal gland, invasion by the tumor to the left renal vein, the inferior vena cava, the inferior phrenic vein, the left suprarenal vein, the right atrium, the left renal pelvis and the left ureter, thrombotic occlusion of the inferior vena cava and its tributaries into both femoral veins, chronic passive congestion of the liver, calcific nodule in the spleen, pyelitis of the left kidney, cystitis and arteriosclerosis, adenomatous hypertrophy of the prostate, bilateral hydrocele, cerebral edema and cardiac hypertrophy.

The cause of death was considered to be adenocarcinoma (hypernephroma) of the left kidney.

## COMMENT

Recent observations in World War II and in civilian practice have made physicians more aware of occlusions of the inferior vena cava. In the last ten years at Kings County Hospital 151 cases of hypernephroma have been noted; 104 of the patients were males, and 47 were females. It was surprising to note the relative paucity of case reports in the literature in the last ten years as compared with those in previous years. Attention should again be directed to reemphasize the relative frequency of this clinical picture. Pleasants<sup>1</sup> reported in 1911, after an exhaustive study of the material to that date, that there were 322 cases of obstruction of the inferior vena cava described in the medical literature. In 21 of these the condition was due to carcinoma or hypernephroma of the kidney. Taddei,<sup>2</sup> Squire<sup>3</sup> and others<sup>4</sup> reported cases of obstruction of the inferior vena cava due to hypernephroma extending into the right auricle. However, among all these cases only 1 demonstrated obstruction down to the femoral veins such as occurred in the case described here.<sup>5</sup>

In 1924 Judd and Scholl,<sup>6</sup> of the Mayo Clinic, reported 15 cases of hypernephroma with obstruction of the inferior vena cava. They showed that of 200 cases of renal tumors the renal vein was involved in 45, or 22.5 per cent. Nephrectomy and removal of the plug of tissue from the renal vein and beyond proved the only hopeful approach to treatment at the Mayo Clinic. Donovan<sup>7</sup> resected a short length of the inferior vena cava in removing a hypernephroma of the right kidney.

The cause of obstruction of the inferior vena cava has been thoroughly discussed by Pleasants.<sup>1</sup> He grouped all known cases under the following etiologic factors: (1) thrombosis, (2) new growths arising from the wall of the vessel, (3) invasion of the lumen by growths from without, (4) pres-

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1. Pleasants, J. H.: Obstruction of the Inferior Vena Cava, with a Report of Eighteen Cases, *John Hopkins Hosp. Rep.* **16**:363-548, 1911.

2. Taddei, D.: *Patologia e clinica dei tumori del rene*, *Folia urol.* **2**:638-700, 1908.

3. Squire, J. B.: *Neoplasm of Kidney and Ureter*, Boston M. & S. J. **161**:547-551, 1909.

4. Johnson, S. E., and Stabile, V.: Hypernephroma with Metastases, *Kentucky M. J.* **41**:351-352 (Oct.) 1943. Abeshouse, B. S., and Goldstein, A. E.: Metastatic Malignant Tumors of the Kidney: Review of Literature and Report of Twenty-Three Cases, *Urol. & Cutan. Rev.* **45**:163-186 (March) 1941. Stevens, W. E.: *Diagnosis and Surgical Treatment of Malignant Tumors of the Kidney*, *J. Urol.* **10**:121-134 (Aug.) 1923.

5. Schrag, A. R., and Jordan, F. B.: Unusual Metastasis for Primary Hypernephroma, *Canad. M. A. J.* **53**:168-169 (Aug.) 1945.

6. Judd, E. S., and Scholl, A. J.: Thrombosis and Embolism Resulting from Renal Tumors, *J.A.M.A.* **82**:75-78 (Jan. 12) 1924.

7. Donovan, H. A.: A Malignant Right Kidney Removed at Operation, Together with Short Length of Vena Cava, *Brit. J. Urol.* **17**:107 (Sept.) 1945.

sure from without by neoplastic or inflammatory disease and (5) so-called congenital obliteration of the inferior vena cava.

In general, there are four primary routes of collateral circulation: inferior vena cava to superior vena cava, inferior vena cava to portal veins, portal veins to superior vena cava and inferior vena cava to inferior vena cava around the obstruction. Northway and Greenway<sup>8</sup> have demonstrated the extensive retroperitoneal and paravertebral collateral veins of the inferior vena cava by injection methods.

The cardinal signs of obstruction, edema and collateral circulation also vary in degree. Edema may not develop if death occurs rapidly. Occlusion of the lower third of the inferior vena cava is less likely to be associated with edema than occlusion a block higher up. In typical cases edema lessens with the development of an adequate collateral circulation. It is striking how little functional impairment or discomfort may occur when collateral circulation is well developed. In the patient described here, with an obstruction extending at autopsy from the femoral veins through the iliac vessels and the inferior vena cava to the right auricle, edema persisted for almost four months. It disappeared only in the last week before death. As the edema decreased, the abdominal collateral veins became much more prominent.

When the obstruction extends high enough to obstruct the hepatic veins, ascites or, more rarely, jaundice may develop. In the present instance, although the tumor thrombus extended into the right auricle there was a channel alongside the thrombus enabling the hepatic veins to empty.

In differentiating obstruction of the inferior vena cava from obstruction of the portal vein there are a number of helpful points. Unless the hepatic veins are obstructed, the collateral circulation about the umbilicus is seldom as well defined in the former as in the latter. A caput medusae is a rarity. The collateral veins in obstruction of the inferior vena cava predominate along the lateral region of the abdomen, the lateral area of the chest, the back and the iliac and inguinal regions. In obstruction of the portal vein the collateral veins tend to group near the midline, particularly between the umbilicus and the xiphoid process. Hemorrhoids or esophageal varices are not ordinarily present in obstruction of the inferior vena cava. However, when the obstruction involves the left renal vein, a varicocele on the left side which persists when the patient is in a supine position is positive evidence in its favor.

A last supplementary differential aid, as demonstrated in this case, is the performance of venography, which may demonstrate the lowermost point of obstruction and the collateral circulation.

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8. Northway, R. O., and Greenway, C. D.: Vena Cava and Its Collateral Circulation, *Univ. Hosp. Bull., Ann Arbor* 10:67-69 (Sept.) 1944.

When distended collateral veins are noted on the abdomen, the possibility of an obstruction existing in the inferior vena cava must be entertained. A consideration of the location of the main collateral veins often enables the differential diagnosis from obstruction of the portal vein to be made. In this connection, the frequency with which hypernephroma involves the inferior vena cava is of great importance.

#### SUMMARY

1. A review of the literature reveals over 400 cases of obstruction of the inferior vena cava.

2. The case reported demonstrates the possibility of confusing cirrhosis of the liver with obstruction of the inferior vena cava because of dilated abdominal veins.

3. The unusual extension of thrombosis involving the femoral veins up through the inferior vena cava to the right auricle due to hypernephroma is reported.

4. It is important in all cases of dilatation of the abdominal veins to rule out the diagnosis of obstruction of the inferior vena cava. More extensive use of venography, with abdominal compression as a diagnostic adjunct, is to be encouraged.

135 Fenimore Street (Dr. Fisher).



## PNEUMONIA ASSOCIATED WITH ACUTE SALMONELLOSIS

Report of a Case of Salmonella Bronchopneumonia  
and Fourteen Cases of Interstitial Pneumonia

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IN A RECENT report<sup>1</sup> of an outbreak of food poisoning due to *Salmonella montevideo* in an army general hospital in North Ireland note was made of bronchopulmonary involvement in 19 (6 per cent) of the 350 persons affected. One of the patients had frank bronchopneumonia, with sputum which contained the *Salmonella* organism. Others had interstitial pneumonia, and their sputum did not contain the organism. The cases in which there were respiratory manifestations are given more detailed consideration in the present communication.

The outbreak affected 350 persons in a three day period from April 11 to 14, 1944. The immediate source of infection was rice pudding allowed to stand at kitchen temperature for twelve hours or more, and the evidence indicated that the cook who prepared the pudding was a carrier of the organism. Besides the aforementioned bronchopulmonary changes, the clinical manifestations included pronounced gastrointestinal upset, severe prostration and toxicity, high fever, herpes febrilis (15 per cent), bacteremia (2 cases), neuritis, cutaneous lesions (urticaria and subcutaneous nodules) and an asthenic phase. There were no deaths. Agglutinins against the *Salmonella* organism (in titers up to 1:800) and against sheep's red blood cells (in titers up to 1:512) were found in the serums of some of the patients tested.

Of the 19 patients with bronchopulmonary manifestations, 4 had mild cough during or shortly after the gastroenteritic phase of the

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1. D'Albora, J. B.; Ingegno, A. P., and Edson, J. N.: Outbreak of Food Poisoning Due to *Salmonella Montevideo* in an Army General Hospital, J.A.M.A. 129:10 (Sept. 1) 1945.

illness. There were no clinical or roentgenographic evidences of pneumonia, and the condition was interpreted as bronchitic.

One patient had definite bilateral bronchopneumonia, with sputum which contained *S. montevideo*. His history follows.

REPORT OF A CASE OF SALMONELLA BRONCHOPNEUMONIA

Private F. T. R., a white man 21 years old and belonging to the Field Artillery, was admitted to the surgical service of the 79th General Hospital on March 2, 1944, because of internal derangement of the left knee. An arthrotomy was performed on April 4, 1944. Except for an occasional rise of the temperature to 99 F. there was no fever or gastrointestinal disturbance from March 21 to April 12, 1944. On

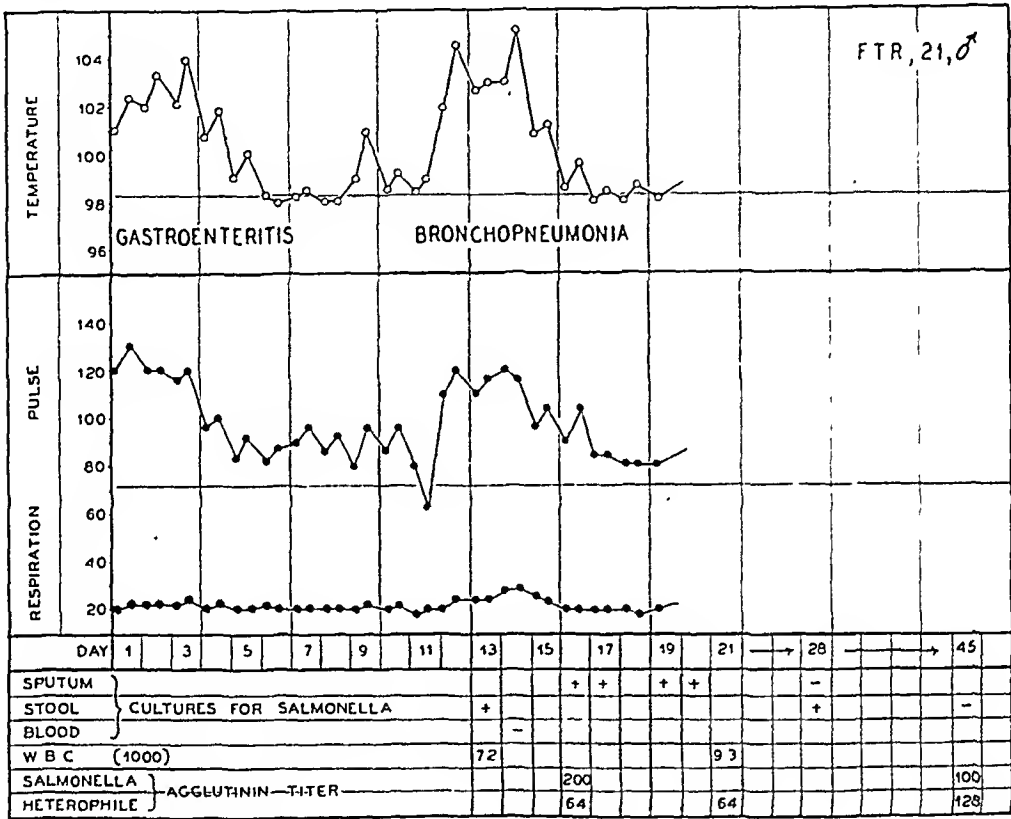


Fig. 1.—Temperature chart and salient laboratory findings in a case of salmonella bronchopneumonia.

April 12 at 2 a.m., nine hours after a supper which included infected rice pudding, diarrhea, abdominal cramps, headache, general malaise, nausea and vomiting suddenly developed. The patient became extremely toxic, with the temperature going as high as 104 F. on the third day. Herpes labialis appeared. There were five watery stools the first day, and the diarrhea lasted five days in all.

After an initial febrile period of five days, fever and toxicity abated for three days although moderate tachycardia continued. There was then mild fever for two days. On April 22, ten days after onset of the gastroenteritis, the patient complained of chilliness, severe generalized headache (especially frontal), general aching, cough and sharp pain in the upper left anterior part of the chest exaggerated by deep breathing and cough. The temperature rose sharply, reaching a maximum of 105.2 F. three days later (fig. 1). Examination revealed severe toxicity and prostration, tachycardia and moderate respiratory difficulty. There was an impaired note, with high-pitched bronchovesicular breath sounds and a few crepitant rales,

over the left lung anteriorly. The sputum became frankly bloody. A roentgenogram (fig. 2*A*) on April 24 showed a bilateral bronchopneumonic process, especially in

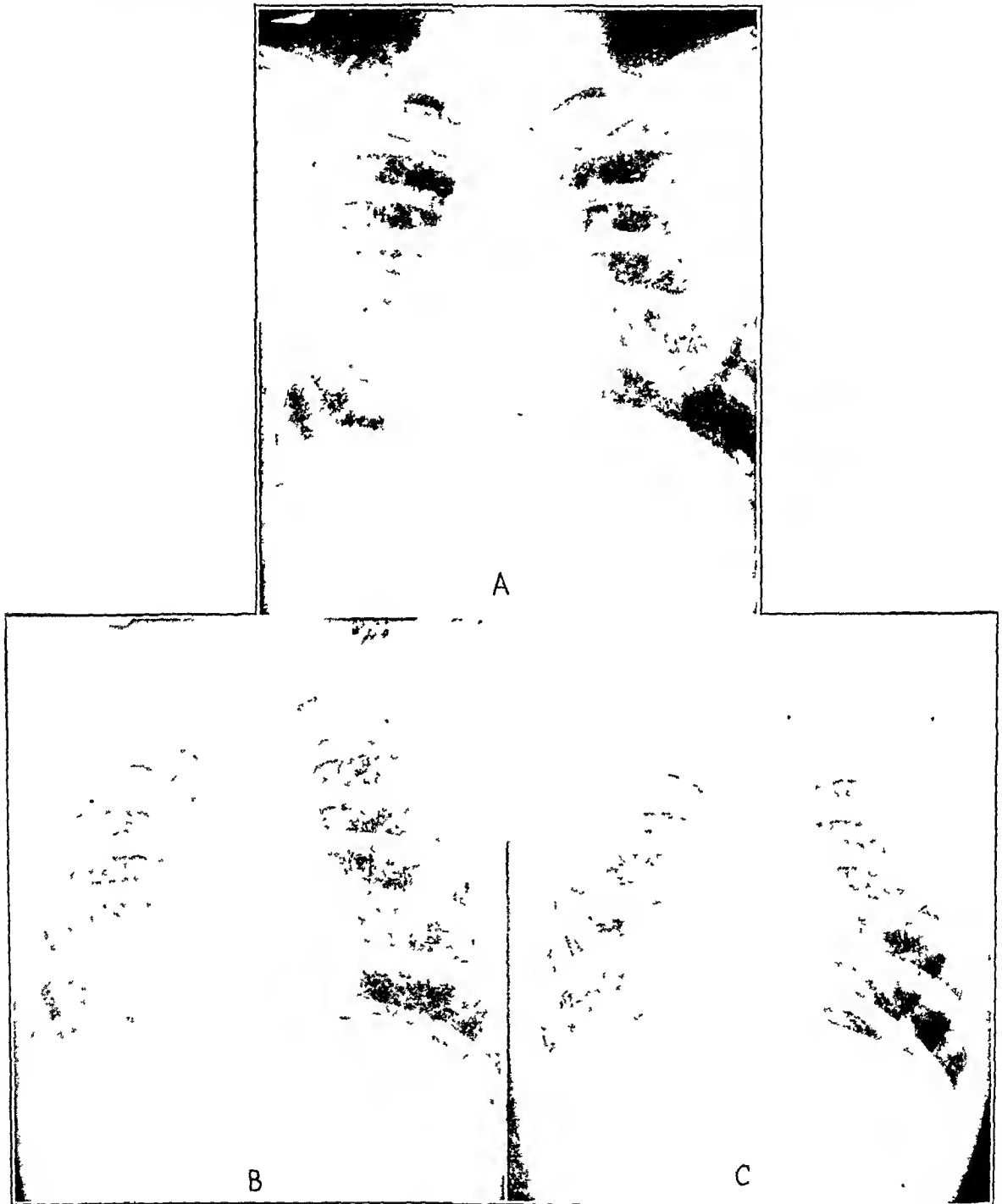


Fig. 2.—*A*, *Salmonella* bronchopneumonia (third day). The process is bilateral, with a confluent patch in the left lower pulmonary field. The pleura on the left is thickened. *B*, same patient on the seventh day. There is partial resolution of the bronchopneumonic process. Pleuritis is still evident. *C*, same patient on the thirteenth day. There is almost complete resolution.

the lower left pulmonary field, where there was a large confluent patch. The pleura on the left was thickened, and interstitial changes were seen on the right

The stool contained *S. montevideo*, and four cultures of the sputum made between April 27 and May 1 also yielded the organism. The white blood cell count and the differential count were within normal limits. On April 27 the serum showed *Salmonella* agglutinins in a titer of 1:200 and heterophile agglutinins (to sheep's red blood cells) in a titer of 1:64.

The patient was severely ill for five days, with hemorrhagic sputum and with severe pain in the left side of the chest. For three of these days the temperature ranged between 103 and 105.2 F. The temperature then fell rapidly to normal on the seventh day. The respiratory symptoms subsided considerably although the pain in the chest was troublesome for a week. Three subsequent roentgenograms taken up to a month later (figs. 2B and C) showed progressive resolution. The last of these, taken on May 23 (not illustrated), showed complete resolution. The sputum remained frankly bloody for about a week and then became mucopurulent and scant. On May 9 culture of the sputum showed it to be sterile although the stool still contained the *Salmonella* organism. A month after the onset of the respiratory complication there were still slight cough and slight pain in the left upper part of the chest. At this time *Salmonella* agglutinins in a titer of 1:100 and heterophile agglutinins in a titer of 1:128 were found in the serum. At no time was the spleen palpable and there were no cutaneous lesions analogous to rose spots. However, an interesting symptom in this patient was the appearance on April 23, at the height of the bronchopneumonic episode, of three small subcutaneous nodules on the anterior aspect of the left thigh and one on the volar aspect of the right forearm. The former disappeared in a day, but a month later the one on the forearm was still present. It was 2 to 3 mm. in diameter, slightly tender but not discolored, and it was attached to fascia but not to the overlying skin.

During the gastrointestinal phase of his illness the patient received 57 Gm. of sulfaguanidine over a three day period, with no obvious effect on the course of his illness. Treatment was otherwise entirely symptomatic. Experience with other patients in the outbreak had not demonstrated any appreciable effect on the infecting organism by either sulfaguanidine or sulfadiazine. Hence neither sulfonamide was given during the period of bronchopneumonia.

The remaining 14 patients reported on in this paper had clinical and roentgenographic evidence of interstitial pneumonia. The main features are summarized in the appended tabulation.

*Salient Findings in 14 Patients with Interstitial Pneumonia Accompanying  
Acute Salmonellosis Due to Salmonella Montevideo*

Acute gastroenteritis . . . Initial phase in all. Lasted 2 to 8 days. Stool cultures positive for *S. montevideo*  
 Quiescent interval between gastroenteritic and bronchopulmonary phase . . . Present in 8 cases, lasting 1 to 4 days. In 6 the two phases overlapped  
 Symptoms . . . Recurrence or exacerbation of fever and toxicity in all. Cough in 13 cases. Expectoration in 8 cases (in 4 mucoid, in 4 bloody or blood streaked). Chest pain in 3 cases  
 Pulmonary signs . . . Found in 11 cases, generally mild. Rales and changes in breath sounds and resonance  
 Duration of bronchopulmonary phase . . . 4 to 14 days, average 10 days. Fever lasted 3 to 10 days  
 Sputum cultures . . . Done 1 to 3 times in 8 cases. All negative for *Salmonella*. Usual mouth organisms  
 Blood cultures . . . Positive for *Salmonella* in 2 of 8 patients tested  
 Blood counts . . . Not characteristic  
 Serum *Salmonella* agglutinins . . . In titers ranging from 1:50 to 1:800  
 Heterophile agglutinins (8 cases) . . . In titers ranging from 1:32 to 1:256  
 Roentgenologic findings . . . Patchy or diffuse interstitial pneumonitis in all. Bilateral in 8, on right side only in 6. Partial consolidation in 2. Pleuritis in 1. Resolution complete within 2 weeks in almost all

All the patients were young white men who had been hospitalized for a variety of reasons. They were all afebrile prior to the outbreak of *Salmonella* infection. In all the initial acute gastroenteritic phase of

the illness was typical of what occurred in the general outbreak. There was an explosive onset eight to fifty hours after ingestion of the infected rice pudding, with fever, toxicity, prostration, abdominal cramps and watery diarrhea. This phase lasted two to eight days.

In 8 of the 14 cases there was then a quiescent interval of one to four days, characterized by absence or considerable diminution of fever, toxicity and gastrointestinal complaints. There then followed a secondary rise in the temperature, increased toxicity and bronchopulmonary complaints, which came on five to nine days after the onset of the illness. In the remaining 6 cases the quiescent interval was not as clearly defined. There was an overlapping of the course of fever and the gastrointestinal and bronchopulmonary symptoms, although in some the appearance of pulmonary symptoms was accompanied with an exacerbation of the fever and toxicity. In 2 of these the blood cultures yielded the *Salmonella* organism. One patient, after being afebrile for a day, had a recurrence of fever, and although he had no symptoms or physical signs of pulmonary involvement, there was definite roentgenologic evidence of interstitial pneumonia. One patient with frank evidence of pneumonia beginning on the second day and lasting for about two weeks had fever for only three days from the onset.

Of the 14 patients, 13 had symptoms and/or signs of pulmonary infection which began two to nine days (in 10 cases five to nine days) after onset of the gastroenteritis. All 13 had cough varying from mild to severe, and in 8 the cough was productive. The sputum was blood streaked or frankly bloody in 4 and mucoid in 4. Three patients had pain in the chest; it was substernal in 2 and over the left side of the chest in the other. There were physical signs in the lungs in 11 patients. Unilateral or bilateral coarse rales were heard in 6 cases. The percussion note was impaired in 4 patients; there were diminished breath sounds in 2 and harsh breath sounds in 1. Crepitant rales were noted in 3 cases. In 7 the physical signs were confined to the right side while in 3 there were no local physical signs of pulmonary involvement. It is thus evident that the regional signs were relatively mild and probably arose mainly from bronchial inflammation. They were in no case suggestive of consolidation. This is in keeping with the nature of the roentgenographic pattern.

The duration of bronchopulmonary manifestations varied from four days to two weeks, with an average of ten days. In the 7 cases in which the high temperature attributable to the pneumonitis could be defined with reasonable clarity it lasted from three to ten days and reached maximums of 100.4 to 105 F. The pulse rate was proportionately elevated except in 1 case, in which it was relatively slow and dicrotic. The patient in this case had a respiratory rate of 36, although in most of the others there was only a mild tachypnea.

The sputum was cultured one to three times in 8 cases. In none could *Salmonella* be found. There were only the usual mixtures of organisms of the mouth, with no one type predominant. In 7 cases the white blood cell count during the bronchopulmonary phase varied from 6,500 to 24,000, with polymorphonuclear cells ranging from 33 to 80 per cent and lymphocytes from 19 to 67 per cent. The changes in the white blood cell count could not be clearly correlated with the clinical course. Nor, in fact, did any distinctive change in the count occur with the onset of the pneumonia when compared with the findings during the period of gastroenteritis. The total white blood cell count and the percentage of polymorphonuclear cells would rise or fall indiscriminately. Generally speaking, however, the more prolonged the illness as a whole,

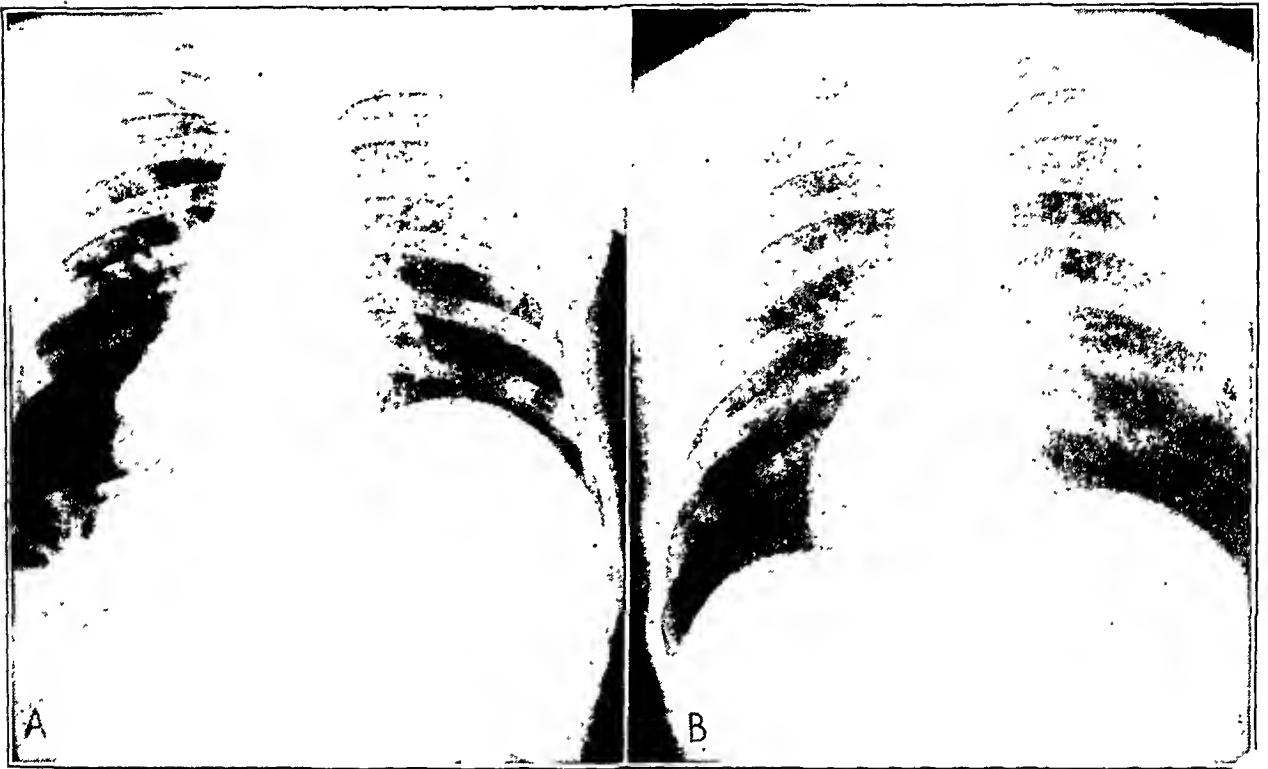


Fig. 3.—*A*, patient with acute salmonellosis. Moderately severe interstitial pneumonia with partial consolidation in the upper lobe of the right lung. *B*, same patient four days later. Resolution is almost complete.

whether or not it was accompanied with pulmonary inflammation, the greater was the tendency to leukopenia and to relative lymphocytosis.

In all the cases cultures of the stool yielded *S. montevideo* at some time during the course of the illness. The onset of bronchopulmonary complaints did not characteristically affect the length of time for which the cultures of the stool were positive. In 2 cases, as already noted, the blood cultures revealed *S. montevideo*. In 6 other cases blood cultures were sterile. In 4 cases urine cultures were also sterile.

*Salmonella* agglutinin titers in the serum ranged from 1:50 to 1:800, and in 8 patients tested heterophile agglutinin titers ranging from 1:32 to 1:256 were found. The time of appearance, the intensity and the duration of these reactions were not characteristically affected by the presence of bronchopulmonary involvement.

Roentgenologic examination of the chest showed changes interpreted as indicative of interstitial pneumonia in all 14 patients. In 8 the changes were bilateral while in 6 the right side only was affected; in 3 the upper lobe of the right lung was affected, in 1 the lower lobe of the right lung and in 4 the entire right side. These interstitial changes were patchy or

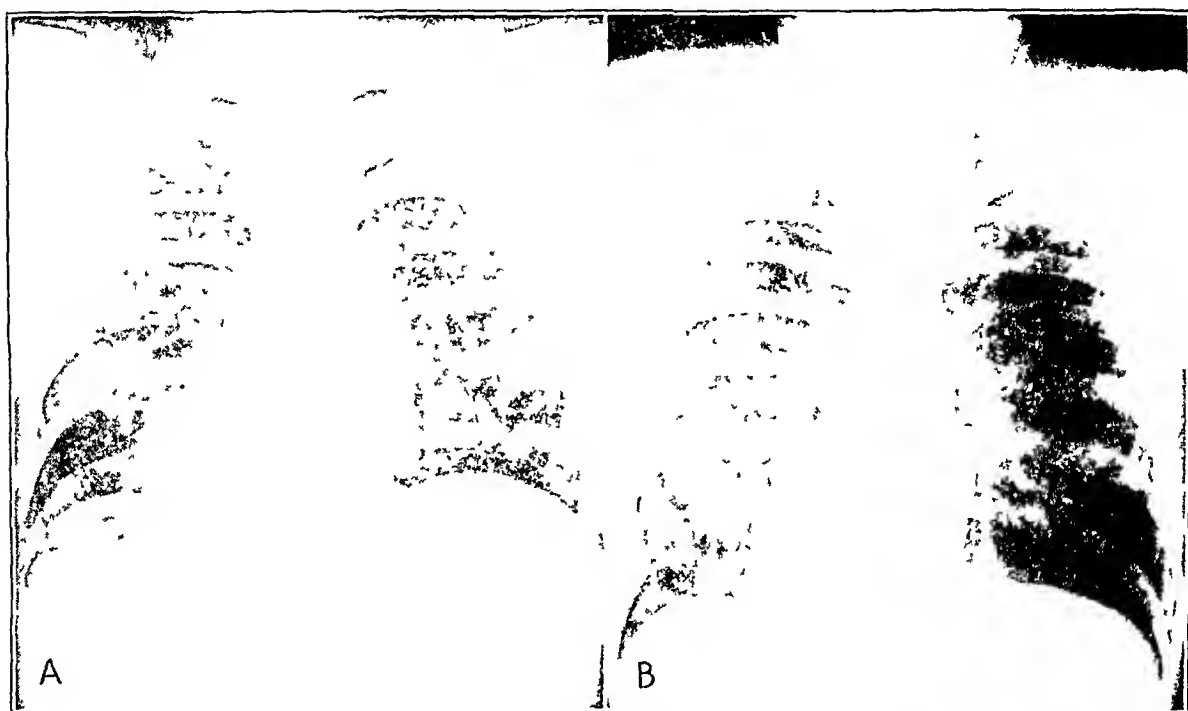


Fig. 4.—*A*, patient with acute salmonellosis. Interstitial pneumonia of the right lung with basal pleuritis. *B*, same patient seven days later. Interstitial and pleuritic changes are resolved.

diffuse and in 2 instances were accompanied with partial consolidation. In 1 patient there was evidence of pleuritis at the base of the right lung. Resolution began within four to seven days of onset and in almost all was complete in about two weeks. There were neither clinical nor roentgenologic evidences of any suppurative complication. The roentgenologic changes found in 2 of the patients are illustrated in figures 3 and 4.

A scattering of other symptoms and signs included asthenia, general malaise, anorexia, herpes labialis, chills, aches and pains, neuritic pains and dysesthesias, sweats and transient urticaria. Sulfaguanidine (39 to 96 Gm.) given during the gastrointestinal phase in 8 patients had no

apparent effect. Sulfadiazine (32 to 42 Gm.) was tried during the pneumonitic phase in 3 patients and was also without result.

#### COMMENT

The variability of the manifestations of salmonellosis has been amply documented in the various reports of outbreaks as well as in reports of isolated cases. Sachs and Antine<sup>2</sup> have recently reviewed the different types and reported five illustrative cases. The three broad groupings of *Salmonella* infection include the gastroenteric type, *Salmonella* fever (clinically simulating typhoid fever) and the septicopyemic type. The last type has come to be recognized as offering a particularly important diagnostic problem, for the cases frequently occur as isolated examples entirely unrelated to any outbreak of gastroenteritis, and almost any viscus or body structure may be affected. The symptoms and signs may thus be extremely variable, depending on the area of localization of the *Salmonella* organisms. Suppurative phenomena are common.

Pulmonary involvement in salmonellosis, however, has received scant consideration. Bullova<sup>3</sup> in 1928 reported a case of infection of the lung with *Bacillus suipestifer* (hog cholera). His patient had consolidation of the middle lobe of the right lung. There was a severe febrile course for five days, with moderate leukocytosis. Sputum and blood cultures and postmortem puncture of the lung yielded a growth of the organism. Cohen, Fink and Gray<sup>4</sup> in 1936 reported an instance of pericarditis, pneumonitis and pleural effusion in a patient whose blood culture twice yielded *S. suipestifer*. There was no note of the organism being obtained from cultures of material from other areas of the body. In 1 of the cases reported by Sachs and Antine the blood culture contained *S. suipestifer*, and the findings at autopsy included septic bronchopneumonia with pulmonary abscesses and empyema. It is not clear from the report whether cultures of material from the local lesions were made.

It may be assumed that true *Salmonella* bronchopneumonia with pulmonary consolidation, such as is reported here, is probably a relatively rare manifestation of salmonellosis. The diagnosis is established by demonstration of the offending organism in the sputum or by puncture of the lung. It is most likely that the organism reaches the lung through

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2. Sachs, J., and Antine, W.: *Salmonella* Infection in Man, *Am. J. M. Sc.* **208**:633 (Nov.) 1944.

3. Bullova, J.: *Bacillus Suipestifer* (Hog Cholera) Infection of the Lung, *M. Clin. North America* **12**:691 (Nov.) 1928.

4. Cohen, L.; Fink, H., and Gray, I.: *Salmonella Suipestifer* Bacteremia with Pericarditis, Pneumonitis and Pleural Effusion: Report of Case, *J.A.M.A.* **107**:331 (Aug. 1) 1936.



the blood stream, although the possibility of aspiration is not entirely excluded. The development of pulmonary suppuration, as in Sachs and Antine's case, represents a more serious complication of the septicopyemic variety of salmonellosis in which there may be widespread abscess formation as in other types of pyemia. Whether or not suppuration complicates the picture the role of the *Salmonella* germ in causing the local pulmonary lesion in *Salmonella* bronchopneumonia is fairly obvious.

The exact relation of the *Salmonella* infection to the more numerous instances of interstitial pneumonia discussed here is not so apparent. Repeated cultures of the sputum failed to demonstrate the organism. The clinical and roentgenologic similarity to so-called atypical pneumonia is evident. Since at the time the outbreak occurred there was also a fairly high incidence of the latter ailment among the troops stationed in the area, it may well be that these cases merely represent the result of an entirely unrelated etiologic agent (virus?), ubiquitously distributed, gaining a foothold in patients rendered susceptible by the debilitating effect of the *Salmonella* infection. Nevertheless, it is also possible that the interstitial pneumonia of salmonellosis in man represents a condition analogous to that occurring in the hog, in which a specific virus is associated with the *Salmonella* infection. Naturally one cannot exclude entirely the possibility, however unlikely, of a remote toxic or allergic effect of the presence in the body of the *Salmonella* organism. The entire question deserves careful consideration in any future outbreak of salmonellosis should the opportunity present itself for exhaustive roentgenologic, bacteriologic and viral investigation.

#### SUMMARY

In an outbreak of acute salmonellosis due to *Salmonella montevideo* 19 patients (6 per cent) had evidence of bronchopulmonary involvement. Four had acute bronchitis. One patient (reported on in detail) had definite bronchopneumonia, with sputum which contained the *Salmonella* organism. The other 14 patients had interstitial pneumonia. The pathogenesis of the interstitial type is unknown, but the clinical and roentgenologic features suggest a viral origin. How frequently interstitial pneumonia occurs in *Salmonella* outbreaks generally and whether or not, if a virus is concerned, it is of a specific type are points worthy of consideration by future investigators.

# CYTOCHROME C THERAPY OF TISSUE ANOXIA IN A CASE OF HEPATOLENTICULAR DEGENERATION

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IN SEPTEMBER 1946 there was admitted to our service a patient with a bizarre clinical syndrome. He presented the symptoms of well advanced parkinsonism, with masklike facies, open mouth with drooling saliva, cogwheel rigidity of musculature, festination of gait, anarthria and a tremor which was present at rest and which was accentuated on intention. The Babinski response was present bilaterally. Clubbing of the fingers and toes was prominent, the skin showed decided pigmentation of generalized distribution and there was edema of the lower part of the legs. The liver and spleen were palpable. Petechiae were present, and there was constant oozing of blood from the gums as well as intermittent microscopic hematuria. Increased bleeding time, total failure of clot retraction and increased capillary fragility, with a relatively normal platelet count were observed. A striking finding was the intermittently bright red color of the venous blood, which resembled arterial blood.

Five months later the patient was found to have developed the Kayser-Fleischer ring of pigmentation at the corneoscleral junctions, said to be pathognomonic of Wilson's disease.<sup>1</sup> Clubbing has not previously been described in this disease, nor have the hematologic findings here presented, though bleeding has occurred in late stages of the disease in association with severe hepatic damage.

The bright venous blood and the presence of clubbing seemed to us to point toward the existence of a relative anoxia. The heart and the lungs were essentially normal, and the vital capacity was unimpaired. In the arterial blood there was normal oxygen saturation of the hemoglobin.

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1. Denny-Brown, D.: *Hepatolenticular Degeneration*, in *Diseases of the Basal Ganglia and Subthalamic Nuclei*, New York, Oxford University Press, 1946, p. 302 (1)-(21).

Spectroscopic study of the blood pigment did not reveal the presence of abnormal forms of hemoglobin. Urinary studies for various metallic poisons and for porphyrins were consistently noncontributory.

We were left, therefore, with the theory of a disturbance of tissue oxidation to account for the patient's anoxia (the "histotoxic type" of anoxia, although we were by no means certain that a toxin was involved rather than an intrinsic metabolic fault). That the patient was anoxic was confirmed by repeated determinations of the arteriovenous oxygen difference, which was found to vary within a narrow range of hypoxia, of which the most extreme was manifested clinically by the bright red color of venous blood. Consistent with the concept of a reduced total of tissue oxidation was the low basal metabolic rate (—24 per cent) in the presence of a presumed normal level of thyroxin as suggested by normal rates of circulation and normal cholesterol levels. We supposed originally that the low level of oxygen utilization by the tissues might account for the widespread manifestations of otherwise unaccountable dysfunctions present.

At this point it may be pertinent to present a simple scheme of tissue oxidations as these are currently understood.<sup>2</sup> In the following formula (adapted from Peters, J. P., and Van Slyke, D.D.: *Quantitative Clinical Chemistry*, ed. 2, Baltimore, Williams & Wilkins Company, 1946, vol. 1, p. 124) we have outlined what is probably the most important pathway, in a quantitative sense, of enzymatic cellular respiration. Each

Substrate  $H_2 \rightarrow 2H^+ + 2e + \text{oxidized substrate}$  (Catalyzed by specific dehydrogenase)

$2H^+ + 2e + \text{Coenzyme I} \rightarrow \text{Coenzyme I } H_2$

$\text{Coenzyme I } H_2 + \text{Flavoprotein} \rightarrow \text{Coenzyme I} + \text{Flavoprotein } H_2$

$\text{Flavoprotein } H_2 + 2 \text{ Cytochrome } Fe^{++} \rightarrow \text{Flavoprotein} + 2 \text{ Cytochrome } Fe^{++} + 2H^+$

$\text{Cytochrome } Fe^{++} + \text{Cytochrome Oxidase } Fe^{+++} \rightarrow \text{Cytochrome } Fe^{+++} + \text{Cytochrome Oxidase } Fe^{++}$

$1/2 O_2 \rightarrow O^{--} + 2(+)$

$2 \text{ Cytochrome Oxidase } Fe^{++} + 2(+) \rightarrow 2 \text{ Cytochrome Oxidase } Fe^{+++}$

$O^{--} + 2H^+ \rightarrow H_2O$

metabolite is oxidized with the catalytic aid of its specific dehydrogenase, with one of the two co-enzymes (diphosphopyridine nucleotide and triphosphopyridine nucleotide) serving to accept the liberated hydrogen ion. The co-enzymes are in turn reoxidized by a reaction involving catalytic reduction of another respiratory enzyme, one of the flavoproteins, which then takes up the hydrogen ions. The flavoprotein (yellow enzyme or cytochrome reductase) is in turn reoxidized by one of the cytochromes.

2. Wynne, A. M.: Intracellular Oxidation and the Biological Transformation of Energy, in Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, ed. 4, Baltimore, Williams & Wilkins Company, 1945, pp. 323-336.

The cytochromes, of which there are at least three, designated *a*, *b* and *c* by Keilin, function in series, each reoxidizing the one before it, until finally the last is reoxidized by cytochrome oxidase, the respiratory enzyme of Warburg. These enzymes differ from those which have gone before in that they do not take up the hydrogen ions. Instead, they shuttle between the ferric and ferrous states, while the hydrogen ions, remaining relatively free within the surrounding aqueous medium, transfer their electric allegiance. The cytochrome oxidase, having been itself reduced by reoxidizing the last of the cytochromes, has the unique power of reoxidizing itself by ionizing molecular oxygen in the surrounding medium. The ionic oxygen then combines with the hydrogen to form water.

In the course of these reactions, there becomes available to the cell the energy predictable from the chemical structure of the original substrate. This energy is liberated in stepwise fashion as each reaction climbs higher in the oxidative scale. The steps involving the cytochromes account for more than two thirds of the total energy released by this chain of reactions, as indicated by the oxidation-reduction potentials of the enzyme systems. Of the energy thus made available, approximately two-thirds are lost in the form of heat (which serves also to maintain body temperature) and one third is utilized in the metabolic activities of the tissue cells. Energy not immediately utilized is stored in the form of energy-rich phosphate bonds, chiefly adenosine triphosphate and creatine phosphate, compounds which function to store and transfer such energy in the form of phosphates to be utilized in the metabolic flux of the earlier catabolism and the anabolism of the foodstuffs and of such vital functions as muscular contraction and glandular secretion.

We had no means of determining where in this scheme our patient's metabolic fault might lie, though such determination would be at least theoretically possible with proper enzymatic studies of tissue in a Warburg apparatus. It did seem, however, that we might influence the kinetics of the entire series of enzymatic oxidative reactions by introducing one or more of these enzymes. Such studies had, in fact, been carried out by Proger and Dekaneas,<sup>3</sup> who demonstrated both in men and in animals that the anoxic effects of breathing 10 per cent oxygen could be eliminated by injections of cytochrome *c*. (In a later study on animals, Scheinberg and Michel,<sup>4</sup> using 3.9 and 2.8 per cent oxygen, were unable to confirm this effect of cytochrome *c*. However, we are of the opinion that the anoxia which they produced was too extreme; cytochrome may improve the utilization of marginal quantities of available oxygen, but it can hardly substitute for that essential gas).

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3. Proger, S., and Dekaneas, D.: The Use of Cytochrome C in Combating Tissue Anoxia, *Science* **104**:389 (Oct. 25) 1946.

4. Scheinberg, H., and Michel, H. O.: The Effects of Cytochrome C in Anoxia, *Science* **105**:365 (April 4) 1947.

We therefore prepared cytochrome *c* (using the method of Keilin and Hartree<sup>5</sup>) from equine hearts, purified it by passage through a Seitz filter and administered it to our patient after preliminary testing. Cytochrome *c* is the only one of the cytochromes which is easily extracted and stable. Minced cardiac tissue is its richest source, from which it is extracted with dilute trichloroacetic acid; it is then fractionated with ammonium sulfate and precipitated with trichloroacetic acid, to be obtained finally as a dark red solution containing approximately 1 per cent protein. The cytochromes are similar structurally to hemoglobin, consisting of an iron-porphyrin complex conjugated with a protein.

In Proger and Dekaneas's experiments 50 mg. of the drug had sufficed for reversing the anoxic effects of breathing 10 per cent oxygen. They claimed that there was absorption of the injected drug by the tissues, with release into the blood stream of any unneeded excess. Such excess was easily determined by the pink color produced in the plasma, which is not unlike the appearance of slightly hemolyzed blood. It was this effect which we aimed at as an indication that a state of sufficiency had been reached. Our patient seemed to require unusually large amounts, since we observed this effect only intermittently while using 80 mg. or more daily intramuscularly.

Since submission of this paper, a report has appeared which serves to explain our difficulty in obtaining a pink color in the patient's serum (Rabinovitch, R.; Elliott, K. A. C., and McEachern, D.: *Cytochrome C: Intravenous Administration in Man*, J. Lab. and Clin. Med. **33**:294 (March) 1948). These authors suggest that the pink color of serum observed by Proger and Dekaneas after injection of cytochrome *c* may have been due to the presence of hemoglobin as a result of slight hemolysis. Cytochrome *c* in serum could be detected by hand spectroscopy only within thirty minutes of injection of 500 mg. In vitro, concentrations of at least 6.5 mg. per hundred cubic centimeters were required for spectroscopic detection. Pinkish discoloration of serum required a concentration of about 20 mg. per hundred cubic centimeters. Discoloration of urine required doses of 200 mg. injected intravenously.

In addition to cytochrome *c*, our patient was given 3 Gm. of sodium succinate daily since succinic acid has been shown by Szent-Györgi to participate in another pathway of oxidative metabolism leading up to the cytochrome series. In this pathway, certain dicarboxylic acids function as oxidation-reduction systems to carry hydrogen atoms from the dehydrogenase system to the cytochrome system. Succinic acid  $\text{CH}_2\text{COOH}.\text{CH}_2\text{COOH}$  is oxidized to fumaric acid  $\text{CHCOOH}:\text{CHCOOH}$ , with concomitant reduction of the cytochrome, and the fu-

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5. Keilin, D., and Hartree, E. F.: *Purification and Properties of Cytochrome C*, *Biochem. J.* **39**:289, 1945.

maric acid is reduced to succinic acid by taking up the hydrogen liberated from the substrate by its dehydrogenase. Proger was able to demonstrate an antianoxic effect of succinate when it was used alone and a potentiating effect when used with cytochrome *c*; these effects were minor in comparison with that of the cytochrome.

We also used large amounts of vitamin B complex, with the intention of increasing the vitamin precursors of the co-enzymes (nicotinic acid) and of the flavoproteins (riboflavin).

#### REPORT OF A CASE

*Case History Prior to Cytochrome Therapy.*—The patient was apparently well until May 1943, when he was hospitalized for five weeks while in the army, with a diagnosis of influenza. This occurred in California; he had not been overseas. From May until his next hospitalization in September, 1943, he lost 30 pounds (13.6 Kg.) in weight, felt weak, tired and nervous, had pains in his legs, joints and muscles and tremor of the hands, slept poorly, had frequent headaches and giddiness and pains in the chest and was restless, anxious and tense. Examination on his admission revealed nothing abnormal except small varicose veins. During his course in the hospital, he complained mainly of numbness of the body and showed no improvement. Studies of the blood and urine were noncontributory, and no fever occurred. The diagnosis in October was severe neurasthenia following influenza, and the patient was granted a medical discharge from the service. Edema of the ankles was noted at this time as well as a prolonged P-R interval, tachycardia and a systolic murmur. In view of these findings, the diagnosis was changed from post-influenzal neurasthenia to rheumatic myocarditis.

After his discharge from the army the patient was able to hold a job as assistant manager of an automobile supply store until Jan. 1, 1946, when he stopped work because of increasing frontal headache, weakness and intermittent fever. Since then he had become rapidly worse, with difficulty in speech, tremor of the left hand, general stiffness and slowing of all muscular movements and drooling from the mouth. Slight swelling of the ankles had been present continuously for the past three years. He was admitted to Winter Veterans Administration Hospital, Topeka, Kans., on Sept. 26, 1946. His weight was 158 pounds (71 Kg.); the maximum weight prior to the initial illness had been 218 pounds (99 Kg.). The family history and the past history were noncontributory; no familial instances of diseases of the liver or brain or of bleeding diseases were uncovered.

On examination, the patient was found to be a well developed and well nourished white man who was 30 years old and over 6 feet (183 cm.) tall and who appeared chronically ill. His face presented a fixed expression, with the mouth open. There were few spontaneous movements of the extremities. Slowness of gait and tremor of the left hand were present. The breath was fetid. The head, neck and chest were otherwise normal. The pulse rate was 70 and regular and the blood pressure 140 mm. systolic and 90 mm. diastolic. (The blood pressure never varied during the patient's subsequent course.) The heart was normal in size, the tones were normal and there was a soft systolic murmur at the apex. The edge of the liver was palpable and smooth, and it was not tender. A small scar was seen on the dorsum of the penis. Clubbing of all fingers and toes was present, manifested by parrot beaking of the nails and by bulbous enlargement of the terminal phalanges. Slight pitting edema of both ankles and of the lower part of the legs and widespread pigmentation of the entire body surface (most notable on the lower part of the legs) were noted. A slight tremor was present in the right hand and a more pronounced one in the left; the tremor was noted to be sometimes of the intention type and sometimes of

the nonintention type. Pill-rolling movements of the fingers and thumb of the left hand were present. Tendon reflexes were exaggerated throughout, and the skin

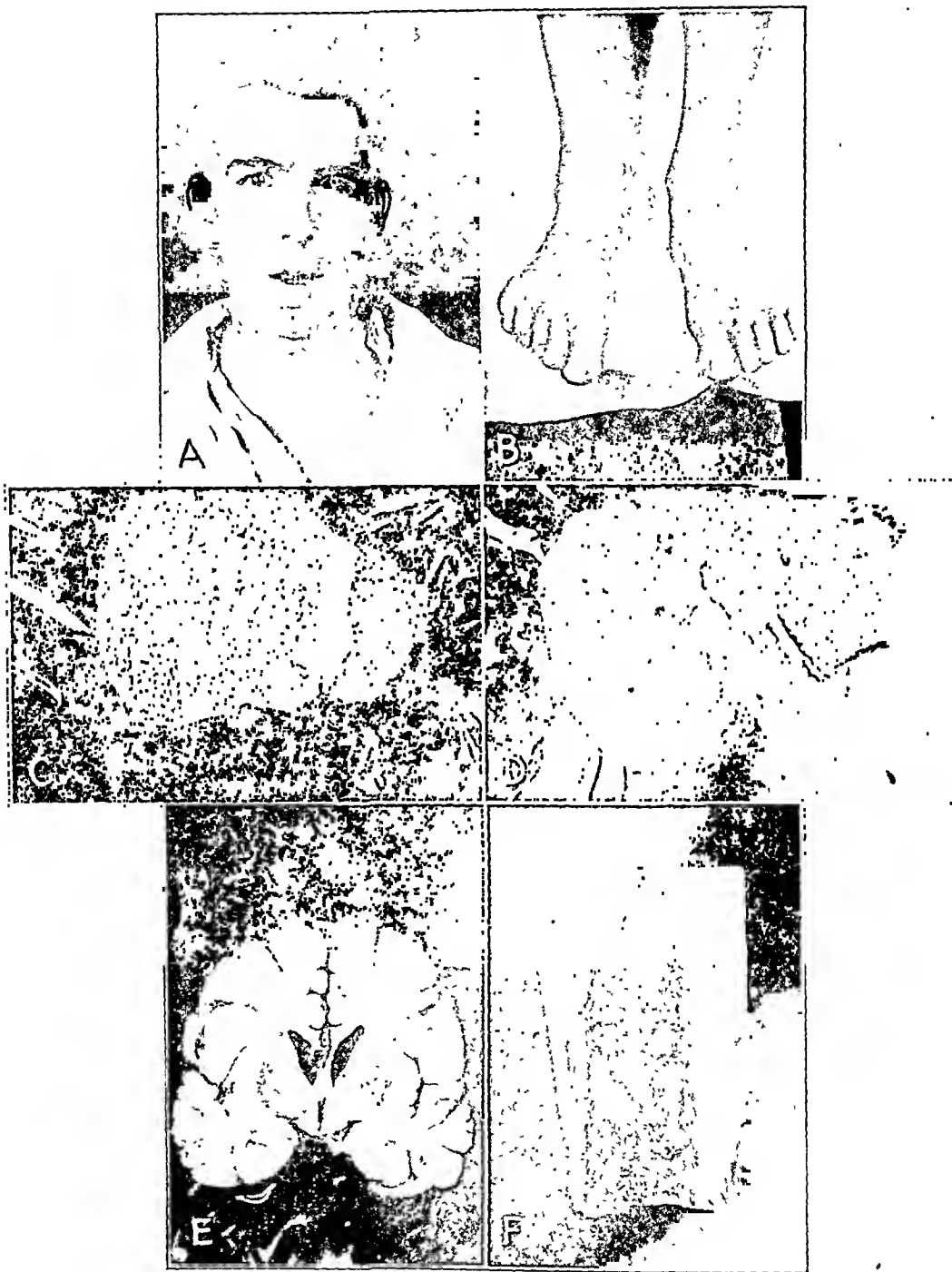


Fig. 1.—*A*, parkinsonian facies. *B*, clubbing of the toes and pigmentation of the skin. Some edema is evident. *C*, ventral aspect of the liver surface, showing extreme degree of nodular cirrhosis. *D*, cut surface of the liver. *E*, brain sectioned through the lenticulostriate nuclei. Note involvement of the internal and external capsules in the widespread degeneration of the lenticulostriate areas. *F*, bone marrow of the femur, with the dark red appearance of hematopoiesis.

reflexes were intact. The Babinski sign was present bilaterally, with dorsiflexion of the great toe and fanning of the others. No changes in the sensory or cranial

nerves were present. There was cogwheel rigidity of the musculature, but weakness of the muscle was not severe. The patient was unable to speak above a whisper. He was passive and uncomplaining and cooperative within his ability. Intelligence appeared unimpaired, but emotional lability was evident.

Bleeding from the gums appeared a few days subsequent to his admission to the hospital and continued intermittently. On October 5 a crop of petechiae was found at the bases and sides of the toes of both feet and a few were found in the palms of the hands; these gradually faded and disappeared in the course of two weeks. Tourniquet compression produced a considerable crop of petechiae at the elbow. The patient stated that he had had previous crops of petechiae during the past year. The prothrombin time was normal. The blood plasma ascorbic acid level was normal (1.1 mg. per hundred cubic centimeters). The circulation time was normal (calcium, 14 seconds). Large doses of vitamins B, C and K had no effect on the bleeding from the gums. Repeated urinalyses revealed intermittent microscopic hematuria, with occasional cellular and granular casts, and traces of albumin. Blood counts showed a moderate anemia, with the red blood cell count averaging 4,000,000 per cubic millimeter and the hemoglobin content 12.5 Gm. per hundred cubic centimeters (color index was approximately 1.0). The hematocrit reading was 38.5 volumes per cent and the corrected sedimentation rate 8 mm. per hour (Wintrobe method). The white blood cell count averaged 6,500 per cubic millimeter; the differential distribution was normal, the eosinophil count varying from 2 to 4 per cent. Platelet counts were 190,000, 180,000 and 150,000 per cubic millimeter. Clotting times were five and a half, eight and six minutes; bleeding times were six and a quarter, five, one and a half and four minutes. The clot retraction in twenty-four hours was repeatedly minimal or absent. A study of red cell fragility showed beginning hemolysis with 0.40 per cent and complete hemolysis with 0.28 per cent sodium chloride. Smears of the sternal bone marrow did not appear unusual. The spleen became palpable, though the palpability may have been missed on initial examination.

The vital capacity was over 100 per cent. The basal metabolic rates were —20 and —24 per cent. Two glucose tolerance tests showed normal fasting blood sugar levels, with a rise to 200 mg. in two hours and a delayed fall, which suggested difficulty in storage or in utilization of glucose. Reactions to Kolmer and Kahn serologic tests were repeatedly negative; a blood culture revealed no pathogenic organisms. The serum protein was 6.2 Gm. per hundred cubic centimeters, with a normal albumin-globulin ratio. The bilirubin content was 0.15 mg. per hundred cubic centimeters. The cholesterol and cholesterol ester values were 167 and 80 mg. respectively and the blood urea nitrogen levels 22.4 and 12 mg. per hundred cubic centimeters. The blood chloride content, as sodium chloride, was 520 mg. per hundred cubic centimeters on two determinations. The serum calcium was 10.8, inorganic phosphorus 3.2 and 2.1 and potassium 16.5 mg. per hundred cubic centimeters. The acid-soluble organic phosphorus content of the serum was 0.6 mg. per hundred cubic centimeters. Studies of the spinal fluid, including culture for tubercle bacilli, revealed no pathogenic organisms, no increase in protein or cell content, a negative reaction to the serologic test for syphilis and a normal colloidal gold curve.

Venous blood oxygen levels at times when the blood was bright red were 15, 15.4 and 14.2 volumes per cent, and when it was blue they were 12 and 12.1 volumes per cent. (Blood oxygen volumes as determined by us represent oxygen combined with hemoglobin exclusive of dissolved plasma oxygen; the figures for total blood oxygen would be approximately 0.3 per cent higher.) On occasions when arterial blood oxygen was not determined simultaneously with the venous oxygen careful determinations with the Fisher electrohemoglobinometer were made and the expected value calculated; these calculated values did not differ appreciably from those ac-



tually determined. Venous circulation times were determined simultaneously to insure a normal rate of circulation at the time of the determinations of oxygen levels. Carbon dioxide—combining power was determined once on red venous blood and found to be 44 volumes per cent and once on blue venous blood and found to be 53 volumes per cent.

Tests for urinary bromides and for various heavy metals<sup>6</sup> did not reveal any. Results of tests for porphyrinuria were repeatedly negative. No creatine was found in two twenty-four hour specimens; creatinine outputs in twenty-four hours were 1.57 and 0.4 Gm. Urea and chloride outputs in twenty-four hours were within normal limits, and the Kepler excretion test for Addison's disease gave a negative result. Phenolsulfonphthalein output was 27 per cent in one hour and 25 per cent in the second hour, a total of 52 per cent.

Concentration tests gave low normal values (1.019). Urine culture yielded *Staphylococcus albus*, believed to be a contaminant. Inoculation of a guinea pig with urine produced negative reactions. Gastric analysis on two occasions yielded normal volumes of free and total acid.

Laryngoscopy disclosed normal vocal cords, with sluggish action, indicating weakness of the musculature but no paralysis. The ocular fundi were normal. The visual fields showed peripheral contraction, more pronounced for color. Kayser-Fleischer rings at the corneoscleral margins were discovered in February after having been looked for and found absent the previous October. Roentgenograms of the chest, stereoscopic roentgen study of the skull and roentgenograms of the bones of the extremities revealed no abnormalities. Electrocardiograms showed prolonged (0.22 second) and slightly varying P-R intervals and minor changes in the forms of the P and T waves. Biopsy of the skin and muscle revealed an increase in the connective tissue of the dermis, vacuolization and thinning of the epithelium, pigmentation of basal epidermal cells (which gave a negative reaction to the test for iron) and thickening of the media of arterioles due to an increase of connective tissue. There were no perivascular infiltrations, nor was there any indication of cellular exudate elsewhere. The muscle fibers had a glazed appearance. An intravenous injection of 5 cc. of adrenal cortex extract failed to change the bright red color of the venous blood.

The patient had no fever during this period of hospitalization except once during the course of an infection of the upper respiratory tract of short duration and terminally. At one time a series of hemorrhagic blebs appeared on the right thigh; cultures and smears of these revealed no organisms, and they slowly healed.

*Subsequent Course.*—On November 29 cytochrome *c* therapy was started, 80 mg. being given daily intramuscularly. The patient seemed to improve clinically within a few days. It is perhaps difficult to state with assurance that the parkinsonian manifestations improved because of the cytochrome *c* therapy, since the intensity of symptoms in parkinsonism is commonly observed to vary with the patient's mood. Furthermore, remissions have been described in cases of Wilson's disease. However, in view of the patient's rapid and unaltered downhill course prior to therapy and the absence of effect of the usual medications used in parkinsonism, we deem his course to have been at least considerably slowed. After two months of continuous therapy, he was able to speak aloud, to feed himself and to walk unassisted. Tremor and cogwheel rigidity disappeared, though plastic rigidity remained. The patient no longer noticed flickering of the motion pictures shown at

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6. Metals of groups II and III were looked for in twenty-four hour samples of urine concentrated ten times. These included mercury, lead, bismuth, copper, cadmium, arsenic, antimony, tin, aluminum, chromium, iron, nickel, cobalt, manganese and zinc.

the hospital, a difficulty formerly present. Edema of the lower part of the legs disappeared (for the first time in three years), and pigmentation and clubbing both diminished notably. The patient's facial expression became more mobile, his mouth remained closed, his tongue was less thickened and no longer encrusted with dried blood and drooling of saliva ceased. The liver became smaller (though this may have represented an advance in the cirrhotic process of Wilson's disease), and the spleen was no longer palpable.

Hemorrhagic manifestations diminished notably but not completely at first. The bleeding time was no longer prolonged (three, two and a half and one second), and the clot retraction was now normal (repeatedly complete in two hours). Clotting times were unchanged (three and one-sixth, four and four seconds). Capillary resistance was improved but still subnormal; bleeding was now confined to oozing from the gum margins, and even this was considerably reduced. Administration of 120 mg. of rutin<sup>7</sup> daily was then added to the patient's therapy on January 27; by February 10 the gums were dry and capillary resistance was normal. A single blood platelet count was 100,000; however, at this time the patient no longer bled. Corrected sedimentation rates were 6 to 16 mm. per hour. Hematocrit readings varied from 35 to 41 volumes per cent.

Icteric indexes of 10 and 7 were found. The blood urea nitrogen was 16 mg. and the nonprotein nitrogen 35 mg. per hundred cubic centimeters. The blood cholesterol level was 153 mg. and the ester level 94 mg. per hundred cubic centimeters. Prothrombin time remained normal. The serum protein was 5.7 Gm., with 3.2 Gm. of albumin and 2.5 Gm. of globulin, per hundred cubic centimeters. The glucose tolerance test now gave a fasting level of 127 mg., with a rise to 250 mg. in one hour and a return to 121 mg. in four hours and to 67 mg. in five hours. The cephalin flocculation test gave a reading of 4 plus in twenty-four hours. The sulfo-bromophthalein test showed 5 per cent retention in twenty-five minutes. The hippuric acid test resulted in excretion of 1.7 Gm. The patient's metabolic rate reverted to

E. T. LOWE— VOLUMES PER CENT OF BLOOD OXYGEN

	Normal	Hemoglobin 12.0 gm. 100 Blood	Red Venous Blood	Blue Venous Blood	Cytochrome Therapy
Arterial Blood.....	19	15.5	15.5	15.0	14.8
Venous Blood.....	12 to 14	10.5	14.2	12.0	8.3
Arteriovenous Oxygen Difference.....	5 to 7	5.0	1.3	3.0	6.5

normal (0 per cent), which indicated an increased consumption of oxygen. The content of acid-soluble organic phosphates in the serum rose from 0.6 to 1.1 mg. per hundred cubic centimeters; this suggested an increase in available stored phosphate bond energy. The carbon dioxide-combining power was now 51 and 58 volumes per cent. Determinations of urobilinogen by Watson's two hour method gave 1.3, 1.8 and 0.9 Ehrlich units per hundred cubic centimeters. Porphyrinuria continued to be absent. The urinary findings were now normal.

The venous blood, the color of which had previously varied from red to a purplish blue, now varied from blue to a deep blue-black. No bright blood was now seen, though the patient was bled hundreds of times. Venous blood oxygen levels were 6.0, 10.6, 8.3 and 3.8 volumes per cent and arterial levels 16.2, 14.8 and 14.1 volumes per cent. The venous blood on days when the low values were recorded was a deep blue-black in appearance, a phenomenon as striking as was the bright red blood originally noted. Representative readings are recorded in the accompany-

7. Griffith, J. Q., Jr.; Couch, J. F., and Lindauer, M. A.: Effect of Rutin on Increased Capillary Fragility in Man, *Proc. Soc. Exper. Biol. & Med.* **55**:228 (March) 1944.

ing table. In column 1 we have indicated the normal arterial and venous oxygen volumes, with the normal difference. In column 2 are the normal values for the hemoglobin level in our patient. It will be noted that in anemias of other than severe grade a physiologic adjustment is reached in which a normal arteriovenous oxygen difference is obtained by increased reduction of the oxygen content of the venous blood. In severe anemias, of course, this adaptive mechanism proves inadequate and further compensatory changes in the form of increased cardiac output and circulation rate occur, bringing about an increased number of round trips per red cell. In the third and fourth columns are listed representative values before cytochrome therapy at times when the venous blood was found to be red and when it was blue. It will be seen that both represent anoxic levels of the arteriovenous oxygen difference and that the color change, the intermittency of which seemed at first inexplicable, actually reflected only a change in degree of the constantly present anoxia. Column 5 lists representative levels during cytochrome therapy. Values during therapy proved always within the normal range of arteriovenous oxygen difference, though there was wide variation within that range.

The figures given in columns 1 and 2 are taken from current physiology texts. A recent study<sup>8</sup> derived lower figures, giving a normal arteriovenous oxygen difference of 4.0 and a normal range of 3.1 to 6.1 volumes per cent. In anemic patients with hemoglobin values between 7 and 13 Gm. the arteriovenous oxygen difference averaged 3.8 volumes per cent, while in those with values of less than 7 Gm. of hemoglobin it averaged 2.6 volumes per cent.<sup>9</sup> These studies were made on mixed venous blood obtained by right atrial catheterization, and arterial blood values were either determined on femoral arterial blood or calculated from hemoglobin values. The figures were obtained under basal conditions, whereas ours were not. It is to be expected that the basal state would result in lower values for the arteriovenous oxygen difference, since the percentage of utilization of available oxygen by the tissues rises with exercise. The blood in our case was obtained by puncture from antecubital veins and from radial arteries.

It is to be noted that our patient's low arteriovenous oxygen differences prior to cytochrome therapy were due to inadequate extraction of oxygen from the circulating blood and not, as in the severe cases of cirrhosis recorded by Keys and Snell,<sup>10</sup> to inadequate oxygenation of the hemoglobin itself. His arterial blood oxygen was such as would be expected from the hemoglobin levels, determined independently.

There was no change in the patient's red blood cell count or hemoglobin value during cytochrome therapy. The white blood cell count increased slightly to an average of 7,500 from the 6,500 noted previously, with a normal differential count. On January 29, after two months of therapy, the first rise in eosinophils was recorded at 16 per cent. This gradually increased to 46 per cent by March 5. This finding was accompanied with no other observable allergic manifestations with the possible exception of what may have been a transient hemolytic reaction, manifested by a drop in the red cell count and in the hemoglobin level for a period of

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8. Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by Technique of Right Atrial Catheterization: Normal Values with Observations of the Effect of Anxiety and Tilting, *J. Clin. Investigation* **24**:326 (May) 1945.

9. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technic of Right Atrial Catheterization, *J. Clin. Investigation* **24**:332 (May) 1945.

10. Keys, A., and Snell, A. M.: Respiratory Properties of the Arterial Blood in Normal Man and in Patients with Disease of the Liver: Position of the Oxygen Dissociation Curve, *J. Clin. Investigation* **17**:59 (Jan.) 1938.

approximately one week; these reverted to normal (for the patient) despite continuation of therapy. When the eosinophilia reached the high level, however, we discontinued the use of cytochrome, with intent to substitute cytochrome of beef rather than that of equine origin. Administration of cytochrome c was discontinued on March 20 and the eosinophil count began at once to drop, being 32 per cent on March 24, 10 per cent on April 2, 6 per cent on April 7 and 2 per cent on April 16. Other medication was continued.

We attempted to use the interim period to reestablish a base line in the absence of cytochrome therapy. Clinically, the patient reverted within a few days to helpless invalidism. Oozing from the gums reappeared despite the continuance of the use of rutin. Edema of the ankles reappeared. The patient ceased speaking aloud. Tube feeding was required for the first time, and breathing became stertorous. Tremor and cogwheel rigidity did not reappear. Aspiration pneumonia involving the base of the left lung occurred, with a rise in the white blood cell count to 15,700. Erythema of the palms of both hands ("liver palms") appeared during penicillin therapy for the pneumonia and it persisted after administration of the drug had been discontinued. The basal metabolic rate fell to -13 per cent. The serum organic acid-soluble phosphorus fraction on April 9 had fallen to 0.8 mg. per hundred cubic centimeters. The blood lactic acid was 24 mg. per hundred cubic centimeters. The cephalin flocculation remained at 4 plus in twenty-four hours, and the icteric index was 13. Bleeding times were three seconds and one second, clotting times were five and five seconds and clot retraction was complete in two and in three hours. Venous blood oxygen levels were 7.5, 13.7, 11.8, 10.7 and 9.8 volumes per cent; the blood became again intermittently bright red.

Since we were afraid that death would occur from choking or from aspiration pneumonia, further attempts to reach a base line were given up. Administration of beef cytochrome c 150 mg. daily intramuscularly was instituted on April 10, three weeks after discontinuance of the equine cytochrome. The patient continued to deteriorate despite this therapy. His venous blood became bright red and remained so and showed constantly high oxygen levels. The red blood cell count and the hemoglobin level did not change, but studies of smears of the peripheral blood revealed myelocytes, many atypical lymphocytes, poikilocytosis and some anisocytosis and basophilia of the red cells. The platelets numbered 170,000. The prothrombin time was moderately prolonged. Respiratory failure developed, and the patient died in coma on April 24.

*Postmortem Examination.*—Gross examination was performed two hours after death by Dr. Manuel G. Gichner. The body was that of a slender white man, approximately 150 pounds (68 Kg.) in weight and 6 feet 1 inch (185 cm.) in height. The skin over the entire body was of a bronze color, with more distinct dark brown pigmentation of the lower part of the legs and of the ankles which faded over the toes and the plantar surfaces of the feet. There was slight edema of both ankles, and the left thigh and calf ranged up to  $2\frac{1}{2}$  inches (6 cm.) greater in circumference than the right. The fingers and toes were moderately clubbed and cyanotic. There was a small penile scar. No lymphadenopathy was found. The subcutaneous fat and muscle were thin.

The heart weighed 338 Gm., with pallor and slight flaccidity of the muscle. The left lung weighed 550 Gm. and the right 390 Gm. Both were rather firm at the bases, and on the left an area of frankly gray consolidation 10 cm. in diameter was seen.

The strikingly nodular liver appeared small in situ and weighed 1,420 Gm. On cut section, the nodules varied from 0.5 to 2 cm. in diameter. They were dark yellow, with occasional hemorrhagic areas. The septums between the modules were broad and firm. The gallbladder and the extrahepatic biliary channels were un-

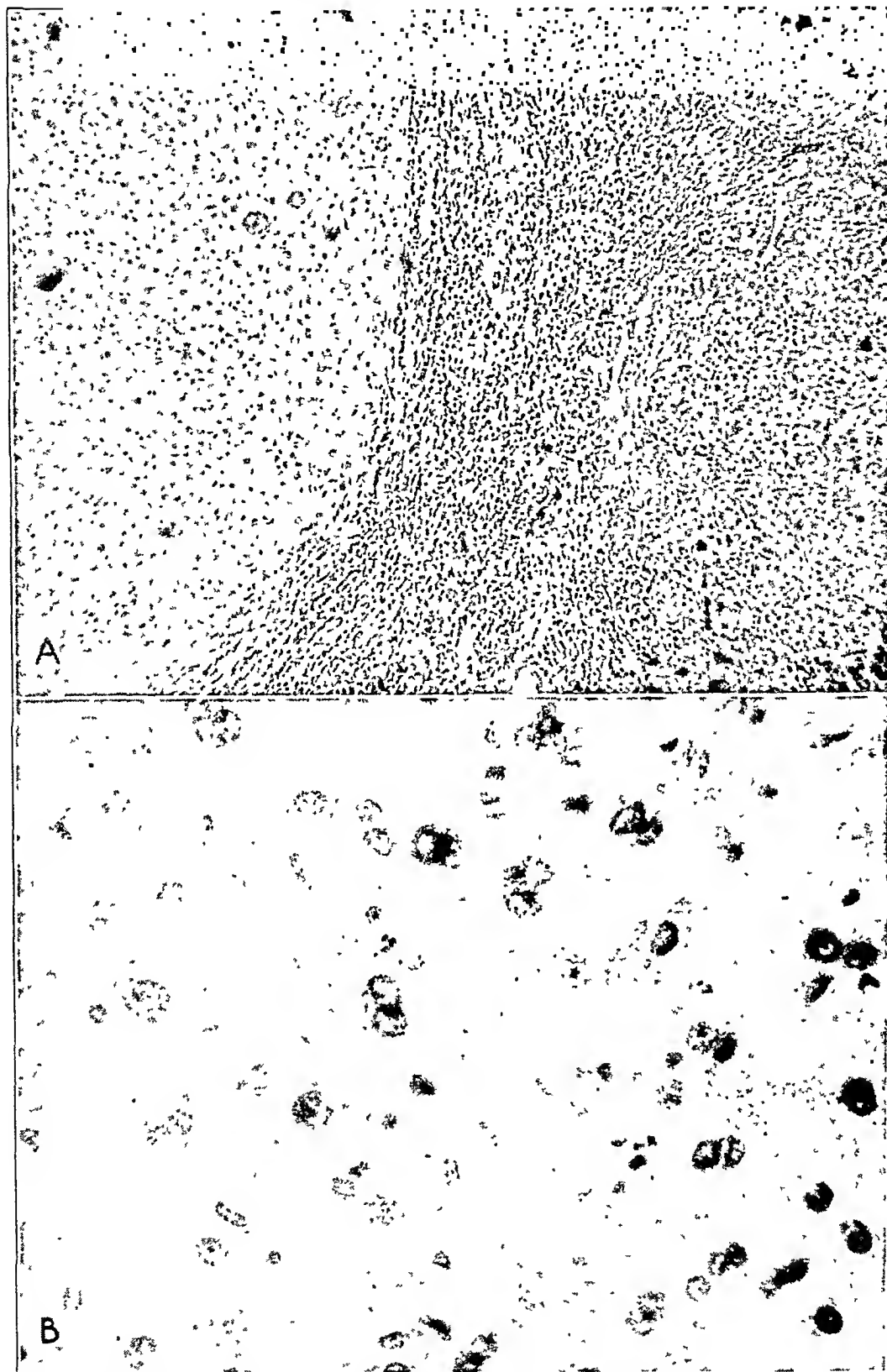


Fig. 2.—Section of the liver. *A*, low magnification, showing adjacent zones of hepatic regeneration, fibrosis with round cell infiltration and hyperplasia of biliary ducts; *B*, high magnification, showing active regeneration of hepatic cells. Note the numerous double-nucleated cells.

changed. The spleen weighed 400 Gm.; its capsule was moderately thickened and wrinkled. Its cut surface had a dull hemorrhagic appearance, with indistinct malpighian corpuscles. The pulp did not scrape readily.

The brain weighed 1,420 Gm. The meninges and the vessels were not visibly altered. In the region of the lenticular nucleus multiple small cavities and softening, with light brown discoloration, were observed. This change, particularly notable in the area of the putamen, extended with diminishing intensity into the adjacent external capsule posteriorly and the internal capsule anteriorly. No gross

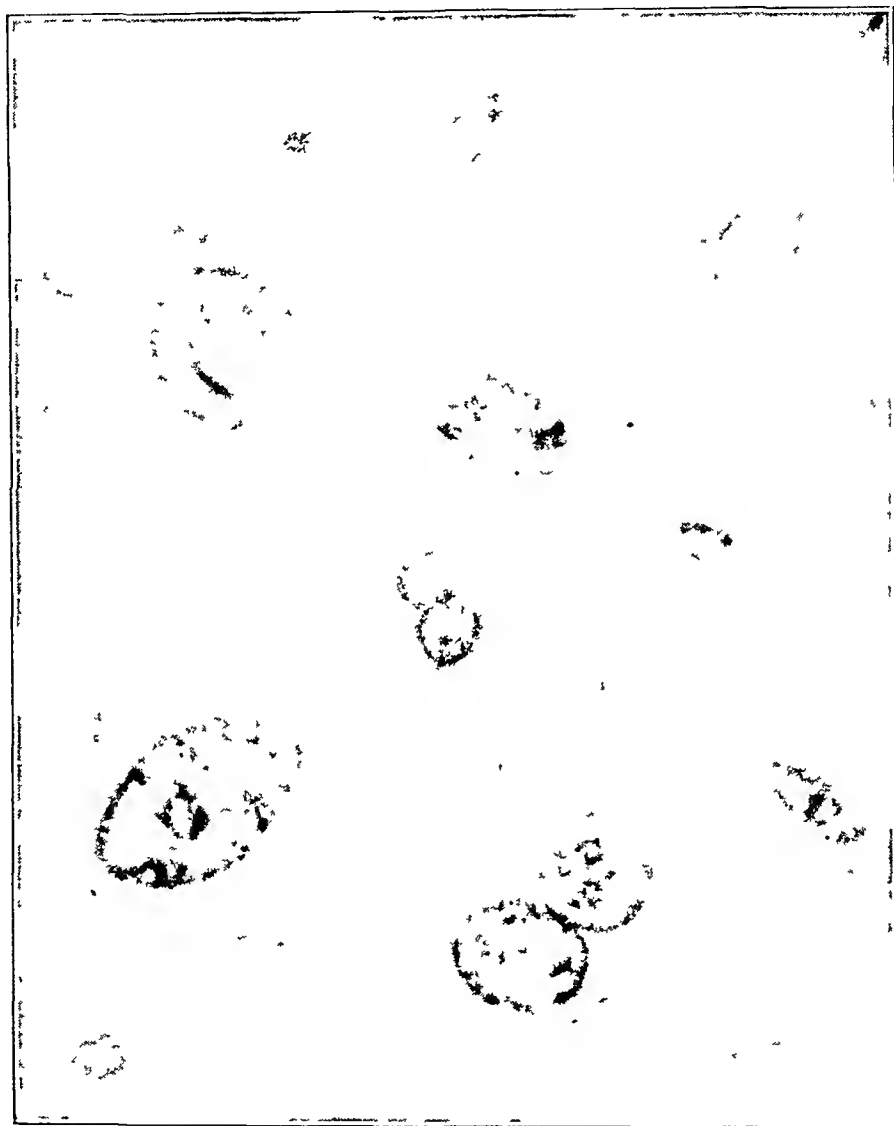


Fig. 3.—Section of the liver, high magnification, showing huge hepatic cells, with cytoplasmic vacuolation and nuclear inclusion particles.

lesions were found in the remainder of the brain or in the upper part of the spinal cord.

The marrow at the junction of the upper and middle thirds of the femur appeared red and hyperplastic, in striking contrast to the usual fatty appearance of marrow in this region.

No changes of significance were noted in the thyroid, adrenals, pancreas, intestinal and urinary tracts, testes or prostate.

*Microscopic Examination.*—This was performed by Dr. Tom R. Hamilton and Dr. Elizabeth U. Corbell. Tissues were fixed in formaldehyde and stained with

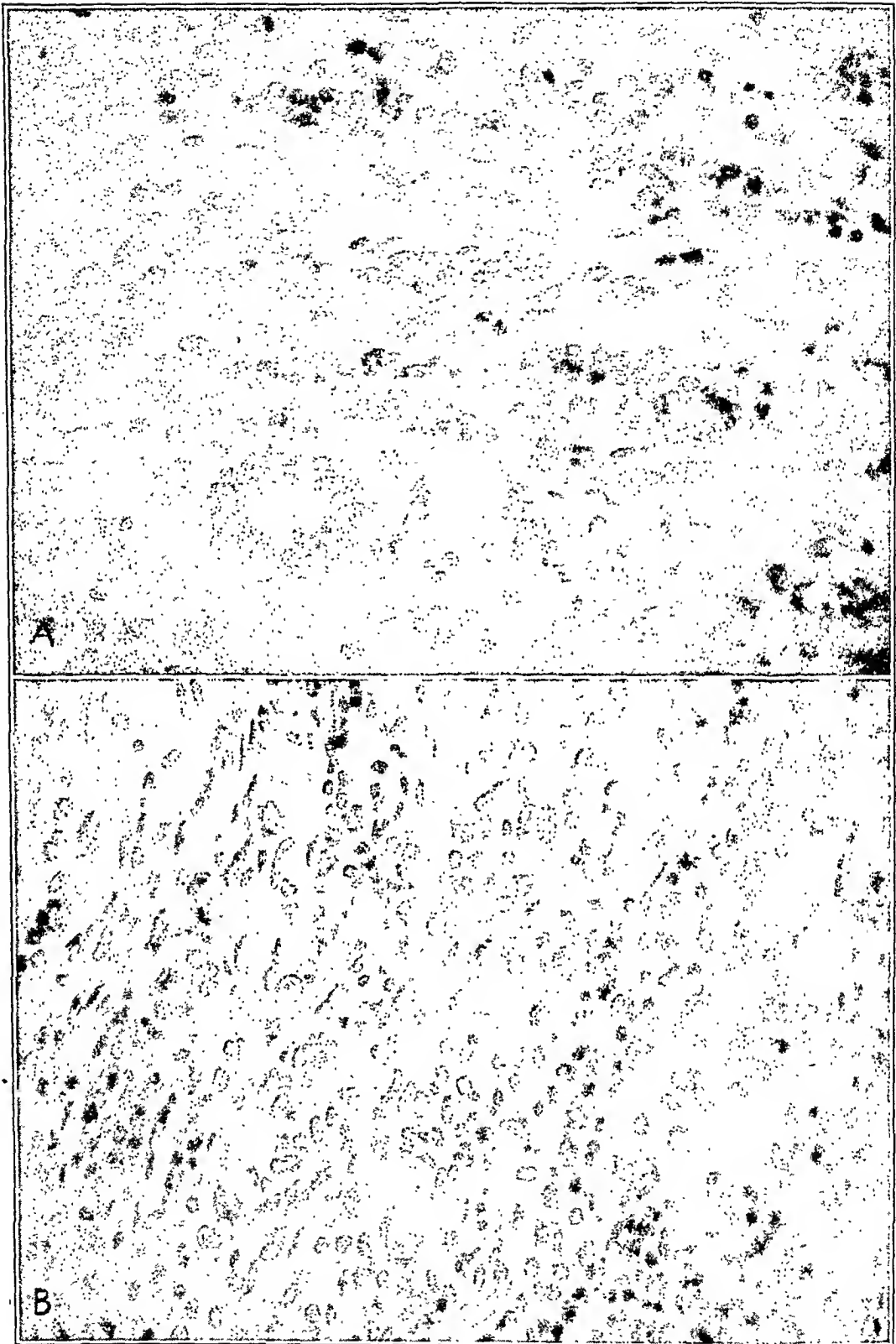


Fig. 4.—Section of the liver. *A*, high magnification, showing hyperplasia of the biliary duct cells; *B*, high magnification, showing nearly adenomatous appearance of hyperplasia of the biliary duct cells.

hematoxylin and eosin. Some sections were stained for fat, glycogen, iron and ceroid.

In sections of the heart, localized vacuolization of the myocardium was noted, especially in the subendocardial region. The myofibrillae and the cross striations of the muscle were somewhat obscure.

The pulmonary sections appeared highly cellular, with polymorphonuclear leukocytes packing the alveolar spaces. Scattered through this exudate were many large pale cells loaded with fat globules as well as numerous pigment-laden macrophages. Some fields were particularly hemorrhagic. Pus cells were found within some of the bronchi. Emphysema predominated in many areas and collapse of the alveoli in others.

The normal lobulation of the liver was lost, and broad zones of dense fibrous tissue coursed through the parenchyma. Numerous small round cells and a few degenerated polymorphonuclear leukocytes were seen in the fibrosed portal spaces. Proliferation of bile ducts was pronounced throughout and suggested an adenomatous process in some areas. In the intervening hepatic nodules there was a remarkable variation in configuration of the cells. Many of the hepatic cells were larger than normal, and a high percentage of them had two or more nuclei. Some of the double and many of the single nuclei were pale, vesicular and four and five times the normal size, while other hyperchromatic, bizarre forms were as much as ten times the normal size. Numerous vacuolated hepatic cells were seen, and small discrete granules appeared in some of the vacuoles. Acidophilic inclusion particles were seen in a few of the large vesicular nuclei. These did not stain with glycogen stains. Nearly all the hepatic cells contained fine fat droplets.

In the spleen cellular fibrous tissue appeared prominent in the pulp, and some swelling of cells lining the sinusoids was observed. The sinusoids contained a moderate number of large round cells and granulocytes.

Cloudy swelling and some tubular necrosis were seen in the kidney. Congestion was prominent. Some thickening of vascular walls was noted in small vessels including capillaries of the glomerular tufts.

Decided reticuloendothelial hyperplasia was noted in the lymph nodes. Hematopoiesis, particularly erythropoiesis, encroaching on fatty marrow was prominent in sections from the femur.

Arrest of spermatogenesis was apparent in the testis, and the interstitial cells of Leydig were less conspicuous than usual. There was a slight increase in connective tissue between the seminiferous tubules, and there was some apparent increase in pigment in the interstitial cells.

In the region of the putamen and the adjacent internal and external capsules the brain tissue had a loose, spongy appearance. Numerous small round cells and gitter cells were seen in the spaces. Moderate glial proliferation was present. The walls of the blood vessels in these areas were thickened. Occasional endothelial cells were vacuolated, and some contained acidophilic nuclear inclusion particles. In other sections of the brain, including the cortex, the perivascular spaces contained rather large quantities of fine golden yellow pigment granules both intracellularly and extracellularly. These deposits were usually found in association with slight perivascular accumulations of small round cells. They did not reveal iron when stained.

The skin and the skeletal muscle showed little significant change, except that the cross striations of the muscle fibers were less prominent than in the biopsy specimens.

The pigment granules and globules described in perivascular tissue in the brain and in the interstitial tissue of the testis were acid fast and were assumed to be ceroid. Other tissues stained by the Ziehl-Neelsen technic and shown to contain



ceroid were adrenal cortical cells, regenerating hepatic cells and occasional Kupffer cells of the liver. Ceroid was not found in striated muscle, lung, pancreas, spleen, lymph node, bone marrow or thyroid.

*Diagnosis.*—The diagnosis was (1) hepatolenticular degeneration, characterized by (a) periportal or toxic cirrhosis, with chronic hepatitis and multilobular regeneration (bile ducts and hepatic cords), and (b) degeneration in the region of the lenticulostriate nuclei; (2) slight degeneration, hydropic and fatty, of the heart and the liver; (3) parenchymatous degeneration and tubular necrosis of the kidneys; (4) slight fibrosis of the spleen; (5) hyperplasia of the bone marrow of the femur, and (6) bilateral lipid pneumonia.

#### COMMENT

Certain pathologic changes referable to anoxia were observed, but they did not seem marked; therapy with cytochrome c may have influenced these processes. Vacuolization in the liver and heart muscle was similar to that observed in various types of anoxia, such as high altitude anoxia,<sup>11</sup> severe anemia<sup>12</sup> and experimentally produced low oxygen tensions.<sup>13</sup> The hyperplastic bone marrow is interpreted as a compensatory response to anoxia, although the effect of cytochrome c therapy is undetermined. Hepatic regeneration was of remarkable degree and is of interest in view of Drabkin's recent report of increased hepatic regeneration in partially hepatectomized rats given injections of cytochrome c.<sup>14</sup> Ceroid pigment, typically found in experimentally induced vitamin E deficiency and dietary cirrhosis in rats, has only recently been observed in human beings.<sup>15</sup>

#### SUMMARY

A case of hepatolenticular degeneration is described which presented certain unusual features believed to indicate tissue anoxia. Treatment with cytochrome c resulted in reversal of these features and in clinical improvement. Fatal relapse occurred when administration of cytochrome c was discontinued because of development of eosinophilia; terminal reinstitution of cytochrome therapy proved ineffective. Autopsy revealed a remarkable degree of hepatic regeneration and other unusual findings.

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12. An evaluation of the vacuolization in anemic anoxia with reference to hydropic as well as fatty change is in progress and unpublished (T. R. Hamilton and G. Chaney).

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# DISREGARDED SEEDBED OF THE TUBERCLE BACILLUS

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THE steady decline in the mortality from tuberculosis has been interpreted as indicating that this disease would in the near future become one of minor significance. This implies that there is a definite ratio, such as was found in the Framingham study,<sup>1</sup> between new cases of tuberculosis and deaths from the disease. Robins<sup>2</sup> pointed out that prior to 1934 there had been no systematic effort made to determine the prevalence of tuberculosis in any large city in the United States and that in surveys made in New York City since 1934 the racial prevalence of the disease has been found to be completely in discordance with the results anticipated from the application of standards based on mortality statistics. His study indicates that the mortality rate and the annual incidence rate are independent of each other and that the prevalence of clinically active tuberculosis is the resultant of the two. Robins<sup>2</sup> and Fellows<sup>3</sup> determined that the number of adults with clinically active tuberculosis annually was between 2 and 3 per 1,000. Robins<sup>2</sup> and Reid<sup>4</sup> were able to determine the "source case" for only a small percentage of these new cases. The unknown source of infection makes the control of tuberculosis the difficult problem that it is. The present study was undertaken to determine the location and the extent of the unknown source of infection, the disregarded part of Greenwood's<sup>5</sup> "seedbed" of the tubercle bacillus.

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From the Laboratories of Pathology, Bellevue Hospital.

Sponsored by the Hegeman Memorial Fund.

1. Final Summary Report, Framingham Monograph 10, July 1924.
2. Robins, A. B.: The Development of Tuberculosis in the Apparently Healthy Adult, *Am. Rev. Tuberc.* **47**:1, 1943.
3. Fellows, H. H.: Serial Chest Roentgenograms of 3,179 Office Employees, 1926-1938, *J. Indust. Hyg. & Toxicol.* **22**:157, 1940.
4. Reid, A. C., in discussion on Robins.<sup>2</sup>
5. Greenwood: *Epidemics and Crowd-Diseases: An Introduction to the Study of Epidemiology*, London, Williams & Norgate, Ltd., 1935.

Routine necropsy protocols contain much information on tuberculosis that is not utilized. In records of this type data relative to the incidence of infection are unreliable, for rarely is sufficient search made for minute tuberculous foci. The major manifestations of tuberculosis as a primary cause of death are well documented. Information relative to caseous foci several millimeters in diameter and to cavity formation is reliable. It is pathologic changes of this type, present in the tissues of persons who died from other diseases, that represent unhealed and often unrecognized tuberculosis from which tubercle bacilli are frequently discharged. The authors regard the caseous focus in the lung as an area of necrotic tuberculous pneumonitis which when it softens and is extruded serves as the source from which tubercle bacilli may be scattered within the lung and to the outside world.

To determine the incidence of deaths from tuberculosis and of unhealed tuberculosis in persons who died from other diseases the necropsy records of Bellevue Hospital on adult patients over 15 years of age have been examined for a ten year period, i.e., 1935 through 1944. Bellevue Hospital was chosen because it is a large public general hospital that is used for teaching purposes by three medical schools. In addition to the usual services in a general hospital, there are a large psychiatric service and a service for the treatment of disease of the chest. To the latter are referred patients with all types of chronic pulmonary conditions. This service acts as a clearing house for tuberculous patients whose residency in the hospital averages about one month.<sup>6</sup> Three fourths of the deaths from tuberculosis on this service occur within one month after the patients' admission to the hospital. A small percentage of the patients with known tuberculosis are cared for by other special services. There is a large necropsy service, with a considerable volume of data available on persons who died from tuberculosis and from various other diseases.

#### PRESENTATION OF DATA

The data obtained from the necropsy protocols are analyzed in relation to age, sex, race, the presence or absence of caseous foci or of cavity formation in the lung, generalized miliary tuberculosis, tuberculosis as a primary cause of death or as an incidental finding in persons who died from other diseases and the clinical diagnosis relative to the recognition of the tuberculosis found at necropsy.

*Table 1.*—In table 1 is presented the incidence of unhealed tuberculosis for the necropsy series as a whole. Proportionately there were more male patients with tuberculosis, except in regard to persons under

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6. Tuberculosis Reference Statistical Year-Book, New York Tuberculosis and Health Association, 1946.

TABLE 1.—Unhealed Tuberculosis Seen in Necropsies on Adults Over Fifteen Years of Age According to Race, Sex and Age  
(Bellevue Hospital 1935 to 1944)

RACE	SEX	AGE											
		15 to 29				30 to 49				50 to 69			
		All Patients	Tuber- culosis	%	All Patients	Tuber- culosis	%	All Patients	Tuber- culosis	%	All Patients	Tuber- culosis	%
All Patients	Total	7,625	1,041	13.7	417	148	35.4	1,906	384	20.1	3,711	409	11.0
	Male	5,423	829	15.4	200	69	34.5	1,304	317	24.3	2,828	360	12.7
	Female	2,202	212	9.6	217	79	36.3	602	67	11.1	883	49	5.5
White	Total	6,688	797	12.2	236	76	32.2	1,520	274	18.0	3,409	359	10.5
	Male	4,859	660	13.7	113	38	33.6	1,073	229	21.3	2,612	317	12.2
	Female	1,829	137	7.3	123	38	30.9	447	45	10.0	797	42	5.3
Colored	Total	937	244	25.8	181	72	39.8	386	110	28.5	302	50	16.5
	Male	565	169	29.3	88	32	36.3	231	88	18.1	216	43	19.9
	Female	372	75	20.8	93	40	43.0	155	22	14.2	86	7	8.1

TABLE 2.—Necropsies on Adults with Unhealed Tuberculosis Showing Nontuberculous and Tuberculous Deaths in Relation to Types of Pulmonary Lesion, Race and Age (Bellevue Hospital 1935 to 1944)

Type of Pulmonary Lesion	Race	AGE											
		15 to 29				30 to 49				50 to 69			
		All Ages	Death Non- tuber- culous	% Tuber- culous	Total Tuber- culous	Death Non- tuber- culous	% Tuber- culous	Total Tuber- culous	Death Non- tuber- culous	% Tuber- culous	Total Tuber- culous	Death Non- tuber- culous	% Tuber- culous
All Patients	Total	1,041	248	793	76.2	148	0	148	100.0	384	52	332	86.5
	White	797	230	567	71.2	76	0	76	100.0	274	47	227	82.9
	Negro	244	18	226	92.7	72	0	72	100.0	110	25	105	95.5
Cavity	Total	793	131	662	83.6	113	0	113	100.0	315	26	289	91.8
	White	618	121	497	80.5	71	0	71	100.0	229	3	206	90.0
	Negro	175	10	165	94.4	42	0	42	100.0	86	3	83	96.5
Caseous focus	Total	152	104	48	31.8	8	0	8	100.0	45	24	21	46.7
	White	130	100	30	23.1	1	0	1	100.0	35	23	12	34.3
	Negro	22	4	18	81.1	7	0	7	100.0	10	1	9	90.0
No cavity or caseous focus	Total	96	13	83	86.5	27	0	27	100.0	24	2	22	91.7
	White	49	9	40	81.7	4	0	4	100.0	10	1	9	90.0
	Negro	47	4	43	91.9	23	0	23	100.0	14	1	13	92.9

30 years of age, and more Negroes than white patients. Unhealed tuberculosis is recorded for both sexes, for both races and for all age groups.

*Table 2.*—The cases of unhealed tuberculosis are analyzed in table 2. In most cases in which tuberculosis was recorded in the necropsy records of Negroes it was the primary cause of death, whereas 29 per cent of the white patients died from diseases other than tuberculosis. This suggests that if a progressive tuberculosis becomes established in Negroes they seldom survive long enough to die from other causes, in contrast to the occurrence among the white race. It does not indicate, however, that persons of the Negro race once infected cannot prevent the infection from progressing. Formation of tuberculous cavities in the lungs of patients who died from disease other than tuberculosis was more frequently noted in persons of the white race.

Caseous foci without cavity formation in the lungs were more frequently mentioned in reports on white patients and were more often an incidental finding. The caseous foci recorded were all at least 5 mm. in diameter, and undoubtedly many smaller foci of this type would have been noted had a greater awareness of their significance been present. That the caseous focus is not an innocuous lesion is shown by the fact that when this lesion was found without cavity formation in the lungs it was associated with death from tuberculosis in 23 per cent of the white patients and in 81 per cent of the Negroes.

Neither cavity formation nor caseous focus in the lungs was recorded in 9.2 per cent of the patients. The number of white patients for which neither was recorded was 6 per cent and the number of Negroes 19 per cent. The greater percentage among the Negroes, with one half of them being under 30 years of age, suggests that small caseous foci in the lungs had been overlooked. This explanation may or may not apply to the white patients since 90 per cent of these were in the older age group. In this group 86.5 per cent died from tuberculosis.

The relation of age to unhealed tuberculosis and to death from this disease is significant. Tuberculosis was the cause of death in all patients under 30 years for whom unhealed tuberculous lesions were recorded but in only one half of the patients over 70 years of age. The latter condition was much more frequent among the white patients.

*Table 3.*—The relation of generalized miliary tuberculosis to the type of pulmonary lesions, to race and to age is presented in table 3. Generalized miliary tuberculosis was present in 18.9 per cent of the patients who died from tuberculosis. It was twice as frequent among Negroes as among white persons. It was recorded least often among patients with cavity formation in the lungs. When caseous foci only were recorded and when neither cavity formation nor caseous foci were present in the lungs there was a high frequency of generalized miliary

TABLE 3.—Generalized Military Tuberculosis in Relation to Type of Pulmonary Lesion, Race and Specified Age Groups  
(Bellevue Hospital 1935 to 1944)

Type of Pulmonary Lesion	AGE											
	All Ages			15 to 29			30 to 49			50+		
	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis
Total	793	150	18.9	148	35	23.6	332	58	17.4	313	57	18.2
All Patients	567	83	14.6	76	10	13.1	227	31	13.6	264	42	15.9
Negro	226	67	29.6	72	25	34.7	105	27	25.7	49	15	30.6
Total	662	61	9.2	113	11	9.7	289	26	9.0	260	24	9.1
White	497	39	7.8	71	7	9.8	206	16	7.7	220	16	7.2
Negro	165	22	13.3	42	4	9.5	83	10	12.0	40	8	20.0
Total	48	23	47.9	8	7	87.5	21	11	52.4	19	5	23.3
White	30	13	43.3	1	1	100.0	12	7	58.3	17	5	29.4
Negro	18	10	55.5	7	6	85.7	9	4	44.4	2	0	....
Total	83	66	79.5	27	17	62.9	22	21	95.4	34	28	82.3
White	40	31	77.5	4	2	50	9	8	88.8	27	21	77.8
Negro	43	35	81.4	23	15	65.2	13	13	100.0	7	7	100.0

TABLE 4.—Data on Patients Who Died With Unhealed Tuberculosis (Bellevue Hospital 1935 to 1944)

Cause of Death	Type of Tuberculous Lesion in Lung	A G E														
		All Ages		15 to 29		30 to 49		50 to 69		Over 70						
		No.	Diag- nosed Clini- cally	%	No.	Diag- nosed Clini- cally	%	No.	Diag- nosed Clini- cally	%	No.	Diag- nosed Clini- cally	%			
Tuberculosis	Total	793	703	88.7	148	143	96.7	332	308	92.8	263	222	84.5	50	30	60.0
	Cavity	662	613	92.6	113	113	100.0	289	278	96.2	220	194	88.2	40	28	70.0
	Caseous focus	48	27	56.3	8	5	62.5	21	14	66.7	15	8	53.3	4	0	0
	No cavity or caseous focus	83	63	75.6	27	25	92.6	22	16	72.8	28	20	71.4	6	2	33.3
Other disease	Total	248	66	26.7	..	..	..	52	20	38.5	147	38	25.9	49	7	14.3
	Cavity	131	53	41.5	..	..	..	26	13	50.0	78	33	42.3	27	7	25.9
	Caseous focus	104	12	11.6	..	..	..	24	7	29.2	62	5	8.1	18	0	0
	No cavity or caseous focus	13	0	0	..	..	..	2	0	0	7	0	0	4	0	0

tuberculosis. In cases of this type it is often difficult to determine the original source from which the dissemination occurred.

The group of 150 patients with generalized miliary tuberculosis was composed of 100 males and 50 females. Proportionately, there was no difference between males and females in either race in regard to the group under 30 years of age, but in the groups over 30 years of age in both races generalized miliary tuberculosis was observed twice as frequently among females as among males. The most frequent occurrence of generalized miliary tuberculosis was in the group under 30 years of age, with the second greatest frequency being found in the group over 50 years of age.

*Table 4.*—The clinical records of all patients with unhealed tuberculosis observed at necropsy were examined to determine whether this disease had been mentioned in the clinical diagnosis. Failure to find tuberculosis listed was interpreted as meaning either that the disease had not been suspected or that if considered it had been relegated to a place of no importance. The principal point of interest in table 4 is the correlation of the clinical diagnosis with the findings at necropsy.

Tuberculosis was diagnosed clinically in 89 per cent of the cases in which it was the primary cause of death. It was diagnosed for 96.7 per cent of the persons under 30 years of age and for 60 per cent of the patients over 70 years of age. It was diagnosed also in but 70 per cent of the patients over 70 years of age who had tuberculosis cavity formation in the lungs. There was a decrease in the diagnosis of tuberculosis with the increase of the age of the patient.

Unhealed tuberculosis present in those who died from other diseases received little clinical attention, for in less than half of the patients with tuberculous cavity formation in the lungs was a clinical diagnosis of tuberculosis recorded.

Perhaps the data from the necropsy series may not be applicable to the problem of tuberculosis in a large community. Nevertheless it seemed worth while to compare these data with those contained in the death registry<sup>7</sup> of the city as a whole for the same period.

*Table 5.*—The patients on whom necropsy was performed at Bellevue Hospital equaled 1 per cent of the white persons and 1.7 per cent of the Negroes over 15 years of age who died in New York city. The data presented in table 5 show that the necropsy series contains a higher proportion of white males and of Negroes of both sexes than the series represented in the city registry. Although there is the same general trend relative to age distribution in the two series, the necropsy series contains a lower proportion of patients over 70 years of age.

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7. The data for the New York city deaths were kindly supplied by the Bureau of Records and Statistics, Department of Health, New York City.

TABLE 5.—*Total Adult Deaths in New York City Registry Compared With All Necropsies on Adults at the Bellevue Hospital According to Age, Race and Sex (1935 to 1944)*

Race and Sex	A G E									
	All Ages		15 to 29		30 to 49		50 to 69		Over 70	
	Total	%	Total All Deaths — New York City	% Deaths — New York City	Total New York City Death Registry	% Death Registry	Total	%	Total	%
Total.....	717,943	100.0	35,098	4.8	138,276	19.2	331,198	46.1	213,370	29.9
White.....	367,946	100.0	14,018	3.8	69,701	18.9	186,872	50.7	97,355	26.6
Male.....	(51.2%)									
White.....	297,198	100.0	13,201	4.4	47,463	16.3	126,102	42.4	110,342	36.9
Female.....	(41.4%)									
Negro.....	27,845	100.0	3,461	12.4	12,008	43.1	10,006	35.9	2,370	8.6
Male.....	(3.9%)									
Negro.....	24,954	100.0	4,328	17.5	9,104	36.4	8,218	32.9	3,304	13.2
Female.....	(3.5%)			All Necropsies — Bellevue Hospital						
Total.....	7,625	100.0	417	5.4	1,906	26.3	3,711	48.5	1,591	19.8
White.....	4,859	100.0	113	2.3	1,073	22.0	2,612	53.7	1,061	22.0
Male.....	(63.7%)									
White.....	1,829	100.0	123	6.7	447	24.4	797	43.6	462	25.3
Female.....	(23.9%)									
Negro.....	565	100.0	88	15.4	231	40.9	216	38.2	30	5.5
Male.....	(7.4%)									
Negro.....	372	100.0	93	25.0	155	41.6	86	23.1	38	11.3
Female.....	(5.0%)									



TABLE 6.—*Tuberculosis as a Primary Cause of Death*

Race and Sex	AGE									
	All Ages		15 to 29		30 to 49		50 to 69		Over 70	
	Total	%	Total	%	Total	%	Total	%	Total	%
Total.....	37,425	100.0	8,786	23.4	15,569	41.6	11,191	29.9	1,876	5.1
White.....	19,281	100.0	2,182	11.3	7,992	41.4	7,910	41.0	1,197	6.3
Male.....	(51.5%)									
White.....	8,528	100.0	2,908	34.1	3,190	37.2	1,874	21.9	561	6.8
Female.....	(22.3%)									
Negro.....	5,618	100.0	1,516	27.5	2,929	52.1	1,069	19.0	74	1.4
Male.....	(15.0%)									
Negro.....	3,998	100.0	2,151	53.8	1,463	36.7	341	8.5	38	1.0
Female.....	(10.7%)		Bellevue Hospital Necropsies							
Total.....	793	100.0	148	18.6	332	41.8	263	33.1	50	6.5
White.....	461	100.0	38	8.2	192	41.6	107	42.7	31	7.5
Male.....	(58.1%)									
White.....	106	100.0	38	35.8	35	33.0	26	24.5	7	6.7
Female.....	(13.3%)									
Negro.....	158	100.0	32	20.2	85	53.8	35	22.1	6	3.9
Male.....	(19.9%)									
Negro.....	68	100.0	40	58.8	20	29.4	5	7.3	3	4.5
Female.....	(8.7%)									

TABLE 7.—Percentage of Tuberculous Deaths in Specified Age Groups

Race and Sex	AGE									
	All Ages		15 to 20		30 to 49		50 to 69		Over 70	
	Total	Tuber- culous Deaths	%	Total	Tuber- culous Deaths	%	Total	Tuber- culous Deaths	Total	Tuber- culous Deaths
Total.....	717,943	37,425	5.2	35,098	8,786	25.0	138,276	15,569	331,198	11,194
White.....	367,946	19,281	5.2	14,018	2,182	15.5	69,701	7,992	186,872	7,910
Male.....									97,355	1,197
White.....	297,193	8,528	2.8	13,291	2,908	21.8	47,463	3,180	126,102	1,874
Female.....									110,342	561
Negro.....	27,845	5,618	20.1	3,461	1,546	44.6	12,008	2,929	2,370	74
Male.....									3,304	38
Negro.....	24,954	3,998	16.0	4,328	2,151	49.7	9,104	1,468	8,218	341
Female.....									1,061	34
Total.....	7,625	793	10.4	417	148	35.4	1,906	332	3,711	263
White.....	4,859	461	9.5	113	38	33.6	1,076	192	2,612	107
Male.....									402	7
White.....	1,829	106	5.8	123	38	30.9	447	35	797	26
Female.....									30	6
Negro.....	505	153	27.9	87	32	36.8	231	85	216	35
Male.....									33	5
Negro.....	372	63	18.2	93	40	43.0	155	20	86	5
Female.....									3	3

*Table 6.*—A comparison of deaths from tuberculosis in the two series is presented in table 6. The proportion of males is higher in the necropsy series. There is a higher proportion of the group under 30 years of age represented in the city registry than in the necropsy series. The trend in age distribution is similar in the two series.

*Table 7.*—The relation of tuberculous deaths to total deaths in the two series is presented in table 7. Proved tuberculous deaths are twice as frequent in the necropsy series as in the city series. The higher percentages in the necropsy series pertain to all but three categories of patients, i.e., Negroes, male and female, under 30 years of age and Negro women between 30 and 49 years of age. The ratio between the necropsy data and the data from the city registry is 1.4 to 1 for the group under 30 years of age and 3.9 to 1 for the group over 70 years of age. Seventy-six per cent of those in the necropsy series under 30 years of age who died from tuberculosis were from the service for the treatment of disease of the chest while in the group over 70 years of age 68 per cent were from other services. It can hardly be argued that the higher proportion of deaths from tuberculosis in the necropsy series is due solely to the fact that the hospital has a large active service for patients with tuberculosis.

*Table 8.*—Since there is considerable agreement between the data from the city registry and the necropsy data and since the mortality, from tuberculosis in the city, based on data from the city registry, has shown a considerable decline in the past two decades, it would seem logical to expect to find a similar trend in the necropsy data. In table 8 are presented the necropsy data from Bellevue Hospital for the two periods of 1920 to 1922 and 1940 to 1942. A comparison of the two sets of data shows little change in the incidence of unhealed tuberculosis. Proportionally there were fewer necropsies on persons under 50 years of age in the later period. This same trend has been reported<sup>8</sup> for other necropsy series in the city. It reflects the trend<sup>9</sup> in the aging of the population.

Samples of a single generation are present in both series. Thus the group 15 to 29 years of age in 1920 to 1922 is represented in the group 30 to 49 years of age in 1940 to 1942. Comparisons of the two samples of generations reveal two points of interest. First, as a generation ages the ratio of deaths from other diseases to deaths from tuberculosis increases. Second, there is a decrease in the ratio of deaths from tuber-

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8. Medlar, E. M.: The Incidence of Pathologically Significant Tuberculosis in Routine Necropsies in Private and Public General Hospitals, New York State J. Med. 47:582, 1947.

9. Dublin, L. I.: Health Problems of an Aging Population, Statist. Bull. Metrop. Life Ins. Co. (no. 12) 27:6, 1946.

culosis to deaths from other diseases in persons with unhealed tuberculosis. These two phenomena suggest that as a generation ages increments of tuberculosis are added and that the decrease of deaths from the disease may be due to changes in the soil rather than to any change in the pathogenicity of the tubercle bacillus. Examination of the clinical histories of persons of the ages of 40 to 60 years who died from tuberculosis shows that in some but not in all cases tuberculosis had been diagnosed prior to the final illness. Examination of the clinical histories of persons

TABLE 8.—*Comparison of Necropsies at Bellevue Hospital for the Years 1920 to 1922 and 1940 to 1942 Relative to Death from Tuberculosis and to Unhealed Tuberculosis in Patients Who Died from Other Diseases*

Age	Total Deaths	Deaths Due to Tuberculosis	Deaths Due to Other Diseases		Ratio of Deaths Due... to Tuberculosis to ... Deaths Due to Other... Diseases Accompanied... With Tuberculosis ....
			Unhealed Tuberculosis Present 1920 to 22 (4)	No Unhealed Tuberculosis (5)	
(1)	(2)	(3)	(4)	(5)	(6) = (3) and (4) ....
Total.....	1,307	191 (14.6%)	83 (6.4%)	1,033 (79.0%)	2.3 ....
15 to 29.....	173 (13.2%)	45 (26.0%)	2 (1.2%)	126 (72.8%)	22.5 ....
30 to 49.....	507 (38.8%)	106 (20.9%)	29 (5.7%)	372 (73.5%)	3.6 ....
50 to 69.....	506 (38.8%)	33 (6.5%)	32 (8.3%)	431 (85.2%)	0.8 ....
Over 70.....	121 (9.2%)	7 (5.7%)	10 (8.2%)	104 (86.1%)	0.7 ....
1940 to 42					
Total.....	2,244	282 (12.5%)	152 (6.8%)	1,810 (80.7%)	1.8 ....
15 to 29.....	88 (3.9%)	31 (46.6%)	...	47 (53.4%)	... ....
30 to 49.....	528 (23.5%)	110 (20.8%)	35 (6.6%)	383 (72.6%)	3.1 ....
50 to 69.....	1,159 (51.7%)	113 (9.7%)	86 (7.4%)	960 (82.9%)	1.3 ....
Over 70.....	469 (20.9%)	18 (3.8%)	31 (6.6%)	420 (89.6%)	0.6 ....

TABLE 9.—*Tuberculosis Among Employees of the Metropolitan Life Insurance Company After Employment (Detected Between 1935 and 1946)*

Length of Employment in Years	All Patients		Patients on Whom a Normal Roentgenogram Was Obtained Previously		Patients Previously Examined by Fluoroscopy	
	No.	%	No.	%	No.	%
Total.....	226	100.0	104	100.0	122	100.0
Less than 1..	15	6.6	10	9.6	5	4.1
1 to 5.....	64	28.3	32	30.8	32	26.2
5 to 10.....	80	35.5	34	32.7	46	37.7
10 to 15.....	44	19.4	18	17.3	26	21.3
Over 15.....	23	10.2	10	9.6	13	10.7

who died from other causes but who harbored unhealed tuberculosis fails to reveal a diagnosis of tuberculosis for any previous illness in the majority of instances. These facts suggest that the tuberculosis observed at necropsy on older persons has not necessarily been carried over from a previous decade.

*Table 9.*—These observations are confirmed by clinical studies of adults on whom normal roentgenograms of the chest have been obtained or who have shown a negative reaction to tuberculin. In table 9<sup>10</sup> is presented the new instances of pulmonary tuberculosis found among employees of the Metropolitan Life Insurance Company in relation to the length of service in the company. The persons in this group had either a normal roentgenogram or a normal fluoroscopic reading of the chest prior to their employment. The average age at the time of employment was 20 years. All the persons were subjected to at least a yearly fluoroscopic examination of the chest. Sixty-three per cent of the patients were found to have the disease between the first and the tenth year after employment, but 10 per cent had been employed over fifteen years. The source<sup>11</sup> of the infection could not be traced to anyone in the employment of the company, and the history of contact with a person with known tuberculosis could be elicited in only 10 per cent of the cases. It is our judgment, based on considerable experience at necropsies, that these infections are new ones acquired in adult life rather than "latent" infections too minute to be detected several years previously. This is a graphic illustration of increments of tuberculosis in an adult population that was as free from demonstrable tuberculosis as it is possible to determine from roentgenographic studies of the chest.

#### SUMMARY OF DATA

Cavity formation or caseous foci in the lungs were present in 90 per cent of the persons with unhealed tuberculosis in the necropsy series. Fifty-six per cent of all patients with cavity formation were under 50 years of age, and death was ascribed to tuberculosis in 93 per cent of this group. However only 71 per cent of those over 50 years of age died from tuberculosis. One sixth of the persons with cavity formation died from other diseases, 80 per cent being over 50 years of age. A clinical diagnosis of tuberculosis was made for 94 per cent of the persons with cavity formation in the group under 50 years of age. A clinical diagnosis was made for 81 per cent of a similar group over 50 years of age when tuberculosis was the cause of death and in only 38 per cent when death was due to other diseases. The latter group represents one seventh of all persons with cavity formation.

The presence of caseous foci without cavity formation in the lungs was recorded in 2 per cent of all necropsies. We regard foci of this type as areas of necrotic tuberculous pneumonitis and as the precursors to cavity formation. Until completely organized they cannot be regarded as "closed" foci and must be considered as a potential source for the

10. The data contained in this table were kindly supplied by Dr. Harold Haynes Fellows, Associate Medical Director of the Metropolitan Life Insurance Company.

11. Fellows, H. H.: Personal communication to the authors.

discharge of tubercle bacilli in the air. One third of the patients with this type were under 50 years of age, 54 per cent of whom died from tuberculosis, and two thirds were over 50 years of age, with death from tuberculosis occurring in only 19 per cent. Of the Negroes, 9 per cent had this type, 77 per cent of these being under 50 years of age; death from tuberculosis occurred in 94 per cent. Of the white patients, one sixth had this type, 72 per cent of these being over 50 years of age; death from tuberculosis occurred in only 18 per cent. If the ratio of patients with caseous foci to those with cavity formation is an acceptable criterion, caseous foci show a greater tendency to soften and excavate in Negroes than in white patients. This may be one reason for the difference in the behavior of the disease in the two races. These caseous foci have not received the attention which they merit, for in only 25 per cent of the cases in which they were described was a clinical diagnosis of tuberculosis made.

While the softening of a necrotic area of tuberculous pneumonitis, with a discharge of the contents through the bronchi, is not a complete protection against massive generalized dissemination of the disease, it seems to be an important factor. Cavity formation in the lungs was present in 83 per cent of the persons who died from tuberculosis, with only 9 per cent having generalized miliary tuberculosis. Of the persons dead from tuberculosis in whom caseous foci were present in the lungs or other tissues, without cavity formation in the lungs, 48 per cent had generalized miliary tuberculosis.

In 40 per cent of the cases involving persons over 50 years of age with unhealed pulmonary tuberculosis this disease was not mentioned in the clinical diagnosis. Of this group, 77 per cent were white males, of whom one half had cavity formation in the lungs. A clinical recognition of the tuberculosis would not have altered the primary clinical diagnosis or the treatment prescribed in the majority of instances. However, failure to recognize the presence of pathologically active tuberculosis precluded steps to lessen the danger of spread of the infection.

If all the persons who died from tuberculosis and all the persons for whom a clinical diagnosis of tuberculosis was made are excluded from the necropsy series, there remain 183 persons (2.5 per cent) with unhealed disease, 40 per cent of whom had cavity formation in the lungs. Expressed in the usual statistical terms, this represents a rate of 1,000 persons with unrecognized cavity formation in the lungs per 100,000 of the population.

The data from the necropsies and those from the city registry agree in most instances as to the age distribution for deaths as a whole and for deaths from tuberculosis. The differences in the two series relative to sex and age are probably due to the composition of the population of

the hospital plus the fact that it is usually easier to obtain permits for necropsy on male patients. Permits for necropsy at Bellevue Hospital are obtained by the resident staff, and success in procuring them rests in no small way on the zeal with which they are sought. Greater effort is exerted to obtain permits for necropsy on patients who had presented difficult diagnostic problems or unusual clinical features. More interest is usually manifested in young adults than in the aged. Whatever selectivity there may be in the necropsy series is due to the clinical interest in the cases and to the ability to obtain permits rather than to the nature of the disease disclosed at necropsy. We believe that the necropsy series represents a fair random sample of deaths in the city. A comparison of the necropsy data and the data from the city registry relative to deaths as a whole in relation to deaths from tuberculosis shows a ratio of 1.4 to 1 in the group under 30 years of age and of 3.9 to 1 in the group over 70 years of age. An impression is gained that the death rate from tuberculosis is too high among Negroes under 30 years of age and is below the actual among all other categories represented in the city registry. This seems plausible, for the causes of death as listed in the city registry are in large part based on the clinical and not on the pathologic diagnosis, and in the city as a whole three fourths of the persons who died were over 50 years of age. Twenty per cent of the patients of this age in the necropsy series who died from tuberculosis had not been recognized clinically as being affected with the disease.

A comparison of the necropsies at Bellevue Hospital for the years 1920 to 1922 and 1940 to 1942 fails to reveal any striking difference in the incidence of unhealed tuberculosis in the two series. A similar comparison of necropsies on young children<sup>8</sup> revealed a decrease of 80 per cent in deaths from tuberculosis between 1920 and 1940. Deaths from tuberculosis at Bellevue Hospital in 1940 to 1942 may not reflect the true situation in New York city, for in recent years a majority of the hospitals have adopted a policy of transferring tuberculous patients to special services as soon as the disease is diagnosed and not a few such transfers are made to Bellevue Hospital. This does not apply to the unhealed tuberculosis present in the groups who died from other diseases, and a comparison of the two series in this respect reveals no significant difference between them. One third of the persons with tuberculosis in the two series were in this group, and the number of these over 50 years of age increased from 63 to 77 per cent between 1920 and 1940. It appears that unrecognized and unhealed tuberculosis is concentrated in the population over 50 years of age; the condition is more often met with among males than among females.

## COMMENT

Whenever the problem of tuberculosis is discussed, it is usual to place great emphasis on the decline in the mortality rate. To argue that the continuity of tuberculosis revolves about the mortality rate is to ignore the essential nature of the pathogenesis of the disease. Today a majority of the persons ill with tuberculosis are restored to a state of clinical well-being, and by proper management they may survive for years to die eventually from some other disease. Throughout their life many continue to shed tubercle bacilli, and it is unwise to ignore these persons for they constitute one part of the seedbed.

There are certain other facts which show that tuberculosis is none too well controlled. In the year 1945,<sup>6</sup> 35 per cent of the deaths from tuberculosis in New York city occurred out of hospital and one third of the deaths took place within one month after the patients were admitted to hospital. Twenty-nine per cent of the patients with tuberculosis left the hospital against medical advice. Clinical relapse of the disease accounted for 23 per cent of the admissions to the hospital. Of the newly discovered cases, 12.4 per cent were first known through death registrations. One half of the patients with tuberculosis were discharged either improved or unimproved. These facts relate to the known part of the seedbed.

Unhealed tuberculosis is seldom found recorded in the records of necropsy on adults under 30 years of age if death was due to some other disease. This suggests that if unaltered in its course progressive tuberculosis is a highly lethal disease in young adults. The finding of unhealed tuberculosis in increasing numbers of persons dead from other diseases, in proportion to those dead from tuberculosis, indicates that a progressive tuberculosis acquired in later life tends to be less explosive in type. It is in this part of the population, i.e., persons over 50 years of age, that tuberculosis is less likely to be suspected. This constitutes the unknown part of the seedbed that the necropsy data indicates contains 1,000 persons with cavity formation per 100,000 of the population.

All that is needed to initiate a new case of progressive tuberculosis is for a few tubercle bacilli to lodge in a favorable place in a lung and in a favorable soil. A larger number of new cases might develop in an environment heavily polluted with tubercle bacilli, but it is also possible to have cases occur from a chance exposure to relatively few bacilli. When there are many unrecognized spreaders of bacilli, chance exposure could occur often and new cases could develop without a discernible source of contact. The experience of the Metropolitan Life Insurance Company relative to the development of tuberculosis among its employees after their employment is an excellent example of such a situation. This appears to be the situation also in New York city, where no source of



contact is found for the majority of the newly discovered cases. This situation mitigates against breaking the continuity of the disease.

Frost,<sup>12</sup> in discussing the control of tuberculosis, proposed the thesis that the tubercle bacillus is losing ground because there are fewer deaths from the disease and because "there appears to be no good reason to doubt that the prevalence of open cases is diminishing at something like the same rate as mortality from phthisis." This depends on what is meant by "open" cases. Cases of minimal tuberculosis used to be considered as "closed" cases, but today this is not so. Careful bacteriologic studies have shown that a considerable number of patients with "arrested" tuberculosis and of persons with tuberculosis "of no clinical significance" discharge tubercle bacilli intermittently. Frost probably did not include these patients in his thoughts of the "open" case. It is the survivors who discharge tubercle bacilli more than the persons who die from the disease who enhance the chance for continuity of tuberculosis. A good parasite, for its survival, establishes itself in a large number of hosts, but only a minority succumb to the invasion. In this respect the tubercle bacillus has done well. With the population over 50 years of age being larger today than it was twenty years ago, the necropsy data suggest that the seedbed for the tubercle bacillus has enlarged and that the chances for its survival are enhanced rather than diminished.

The campaign waged to eradicate tuberculosis in cattle in this country struck at the core of the problem, i.e., the eradication of the seedbed. The core of the problem of tuberculosis in man is the same as that in cattle, but the same plan of attack can hardly be recommended.

Control of tuberculosis, meaning a decrease of the continuity of the disease, requires an intelligent supervision of the seedbed to prevent the return to the soil of those factors which favor the tubercle bacillus. This means a planned follow-up of all persons with unhealed disease, which includes those in whose roentgenograms shadows are revealed regardless of whether the disease is considered active or inactive. Thought also must be given to the socioeconomic factors that favor the disease. In addition an intensified search must be made for a cure, in a pathologic as well as in a clinical sense, of those who have a progressive disease.

The problem of the continuity of tuberculosis, as seen at necropsy, appears formidable. This view corroborates the following statement by Greenwood<sup>5</sup>:

At the worst, looking at the position epidemiologically, we might fear that if a population such as ours were, through the breakdown of the machinery of civilization, again exposed to the environmental conditions of a city slum of the eighteenth

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12. Frost, W. H.: *How Much Control of Tuberculosis?* in *Papers of Wade Hampton Frost: A Contribution to Epidemiological Method*, New York, The Commonwealth Fund, 1941.

or early nineteenth century, the reaction in terms of tuberculosis mortality would be sharper than in the past.

Without doubt it is idle to speak of the conquest of tuberculosis; tuberculosis has not been and so far as one can see never will be conquered. We may, however, reasonably expect a further decline in mortality, provided that our means allow us to improve the general environmental conditions of the people.

#### SUMMARY

Among patients who died from tuberculosis the clinical diagnosis was incorrect six times more often for persons over 50 than for persons under 30 years.

Among patients who died from other diseases, but who harbored tuberculosis which was capable of spreading, there was clinical recognition of tuberculosis in only one fourth.

Tuberculosis tends to be less explosive in type in old persons than in young adults. Older persons can have progressive disease with so few manifestations of illness that they may not seek the advice of a physician. In these circumstances they remain unrecognized spreaders of the infection.

The registration of death from tuberculosis in New York city appears to be below the actual with respect to persons over 50 years of age.

In a high proportion of new cases of tuberculosis in adults in New York city the disease is apparently contracted from unrecognized sources of infection.

Mortality rates, encouraging as they seem, do not indicate either the extent or the location of the seedbed in which the tubercle bacillus resides. The seedbed may well be greater in extent today than it was twenty years ago, for it is largely concentrated in persons, principally men, over 45 years of age, and these are more numerous today than they were a generation ago.

The seedbed must be controlled if the continuity of the disease is to be broken. This requires an intensified search for unknown spreaders of the infection, a more thorough follow-up of known cases of tuberculosis, even if considered "of no clinical significance," a more thorough hospitalization of persons with active tuberculous disease, intelligent action on socioeconomic problems to prevent a return of those factors which favor the propagation of the tubercle bacillus and an intensified search for a cure of the disease in a pathologic as well as in a clinical sense.

The seedbed must be eradicated if tuberculosis is to be eradicated.

## APICAL SYSTOLIC MURMUR

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IN PREVIOUS reports<sup>1</sup> it has been pointed out that the true significance of the relationship of apical systolic murmur to underlying cardiac disease has not received due recognition. The consequences of failure to evaluate properly apical systolic murmur was brought to my attention during the late war, and it is to emphasize the result of underestimating this sign that additional material is presented. While serving with the navy, I saw in consultation large numbers of naval personnel in whom the sole objective symptom was a loud systolic murmur at the apex. In none of the cases was there enlargement of the heart; diastolic murmurs were not heard, electrocardiograms were not abnormal and signs of heart failure were not present. Yet the men and women concerned had been on the sick list for days, weeks or months. To the National Naval Medical Center at Bethesda, Md., which in the first year of the war, at least, was practically the last court of appeal for patients with troublesome conditions, came officers, marines, sailors, Waves and applicants for admission to the navy. Not only had they been examined by physicians in the armed forces but they often brought reports from civilian cardiac consultants. The latter frequently did not appreciate the fact that the stress and strain of war, physical and mental, has no counterpart in civilian life. That the patient's "cardiac function" was good was not proof that organic heart disease was absent or that the function would remain normal under war conditions. Unfortunately, Mackenzie<sup>2</sup> was responsible for the idea that an apical systolic murmur, no matter how loud, was not significant provided cardiac function was good and obvious signs of organic heart disease were not present.

In the South Pacific<sup>3</sup> there were many instances in which men complained of pain in the heart, fatigue and shortness of breath. Heart failure often developed in such instances. On examination it was found that they had definite signs of rheumatic valvular disease, and it was not surprising to discover that in many cases the histories revealed that in civilian life apical systolic murmurs had been a source of worry to their families and had created problems both for private physicians and for

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1. Master, A. M.: (a) Evaluation of Systolic Murmurs, U. S. Nav. M. Bull. 42:307 (Feb.) 1944; (b) Rheumatic Fever in the Navy, *ibid.* 41:1019 (July) 1943; (c) The Problem of Rheumatic Fever in the Navy, Am. Heart J. 27:634 (May) 1944; (d) Apical Systolic Murmurs in Incipient Rheumatic Heart Disease, Bull. New York Acad. Med. 22:535 (Oct.) 1946.

2. Mackenzie, J.: Diseases of the Heart, New York, Oxford University Press, 1925, p. 361.

3. Footnote 1a, b and c.

physicians of insurance companies. At the time the men were examined for induction in the navy the recruiting medical officer had to face the problem of appraising the significance of the murmurs.

In the same area it became necessary, when ships had been sunk and health records lost, to reexamine officers and crew in order to obtain new records. During reexaminations instances of early but definite rheumatic heart disease were frequently encountered. It was found that when the men had been given physical examinations in civilian life and at the time of induction the question of significance of an apical systolic murmur had arisen. Furthermore, half of them gave a history of rheumatic fever.

In World War II the army also had to meet the problem of the apical systolic murmur. Levy, Stroud and White<sup>4</sup> considered it the most frequent, important and difficult problem met during cardiovascular examinations for military service and in the establishment of a diagnosis of organic valvular heart disease. They accepted "moderately loud" or "loud" apical systolic murmur as a cause for rejection of draftees. In civilian life evaluation of the apical systolic murmur is just as important and just as troublesome as it is in wartime. Heart failure may develop in patients with early rheumatic heart disease as a result of emotional stress, prolonged physical exertion, recurrence of rheumatic fever or infection with group A *Streptococcus hemolyticus*. The importance of the problem does not strike home in civilian life with the same dramatic force with which it did during wartime, but the situation arises as frequently and is as difficult to meet. Insurance statistics<sup>5</sup> show that loud apical systolic murmurs, even in the absence of enlargement of the heart, heart failure, diastolic murmurs or abnormal electrocardiograms, are a sign of organic heart disease. When the normally expected mortality rate for persons under 40 years of age was accepted as 100 per cent, the

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4. Levy, R. L.; Stroud, W. D., and White, P. D.: Report of Reexamination of 4,994 Men Disqualified for General Military Service, *J.A.M.A.* **123**:937 (Dec. 11); 1029 (Dec. 18) 1943; Reexamination of 4,994 Men Rejected for General Military Service Because of the Diagnosis of Cardiovascular Defects, *Am. Heart J.* **27**:435 (April) 1944.

5. (a) Bonnett, E. C., and Low, E. A.: A Mortality Study of Systolic Heart Murmurs, *Tr. A. Life Insur. M. Dir. America* (1942) **29**:8, 1943. (b) Grosvenor, F. L.: Mitral Insufficiency—A Limited Experience, Including Etiology, abstracted, *Proc. A. Life Insur. M. Dir. America* **13**:199, 1926. (c) Hunter, A.: Heart Murmurs, *Am. Heart J.* **14**:10 (July) 1937. (d) Johann, A. E.: Apical Cardiac Murmurs, abstracted, *Proc. A. Life Insur. M. Dir. America* **14**:155, 1927. (e) McCrudden, F. H.: Heart Murmurs and Insurance, *New England J. Med.* **204**:598 (March 10) 1931. (f) Rogers, O. H., and Hunter, A.: Mortality Study of Impaired Lives: A. Inflammatory Rheumatism; B. Tuberculosis of Lungs and Blood Spitting, abstracted, *Proc. A. Life Insur. M. Dir. America* **9**:161, 1922; (g) Heart Murmurs—Their Influence on Longevity, abstracted, *ibid.* **6**:173, 1919. (h) Rockwell, T. H.: Experience on Risks with Mitral Regurgitation, *Pract. Med. & Surg.* **38**:347 (Feb.) 1933.

figure was 325 per cent for those with apical systolic murmurs, and when there was a history of rheumatic fever the rate rose to 453 per cent. The Metropolitan Life Insurance Company found somewhat similar figures in a study of mitral regurgitation.<sup>6</sup> Hunter<sup>5c</sup> learned that the mortality rate was 50 per cent higher among manual workers with apical systolic murmur than among "white collar workers." Furthermore, it is not infrequent to find unexpected evidence of a defect of the mitral valve and occasionally even of subacute bacterial endocarditis in patients in whom no symptoms had been noted previously except an apical systolic murmur which had been considered of little or no significance.<sup>7</sup> In fact, valvular disease is often overlooked during life and found only at death.

Since mitral valvular disease develops in 30 to 50 per cent of persons who have had rheumatic fever and since about 20 to 25 per cent of them fall victims to subacute bacterial endocarditis, it is essential that deformity of the mitral valve be recognized at an early stage. In many cases the earliest and only sign of disease of the mitral valve is a loud apical systolic murmur.

From the foregoing observations it should be evident that proper evaluation of a loud apical systolic murmur in the absence of enlargement of the heart, diastolic murmurs, abnormal electrocardiograms and heart failure is of paramount importance in medical practice both in war and in peace. I believe that this murmur should be accepted as evidence of organic valvular heart disease until cardiac abnormality can be disproved. I do not, of course, mean to imply that patients with apical systolic murmur necessarily should be considered invalids. The majority of them will undoubtedly lead perfectly normal lives, but they will not be able to undergo extremes of physical effort or to suffer long or severe emotional stress.

Use of the term "loud apical systolic murmur" here is based on the classification of Freeman and Levine,<sup>8</sup> who divided systolic murmurs into six grades: (1) extremely faint but of appreciable duration, (2) slight, (3) moderately loud, (4) loud, (5) extremely loud and (6) unusually loud. I have considered "loud" all apical systolic murmurs which fall within categories 3 to 6.

The following brief case reports illustrate the manner in which early heart disease may become manifest when the patient is exposed to ad-

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6. Medical Impairments and Mortality: Statistical Charts, Metropolitan Life Insurance Company, Scientific Exhibit of the American Medical Association, Milwaukee, Wis., 1933, chart 5, p. 9.

7. Zeman, F. D., and Siegel, S.: Acute Bacterial Endocarditis in the Aged, *Am. Heart J.* 29:597 (May) 1945.

8. Freeman, A. R., and Levine, S. A.: The Clinical Significance of the Systolic Murmur: A Study of One Thousand Consecutive "Non-Cardiac" Cases, *Ann. Int. Med.* 6:1371 (May) 1933.

verse conditions. The cases are taken from military and civilian experience.

CASE 1.—J. S. A., a boy aged 17, had applied for induction in the navy. The recruiting officer heard an apical systolic murmur which he considered was organic in nature. The patient was rejected, but he was persistent and submitted the opinions of civilian cardiac consultants who pronounced the murmur functional. He was referred finally to the National Naval Medical Center at Bethesda, where I examined him early in 1943. Except for a prolonged systolic murmur at the apex, physical examination, fluoroscopic study and electrocardiograms revealed nothing abnormal. There was no history of rheumatic fever or of infection with *Str. hemolyticus*. However, the heart sound tracing gave evidence of a systolic murmur of prolonged duration from the first to the second sound (fig. 1). This was shown

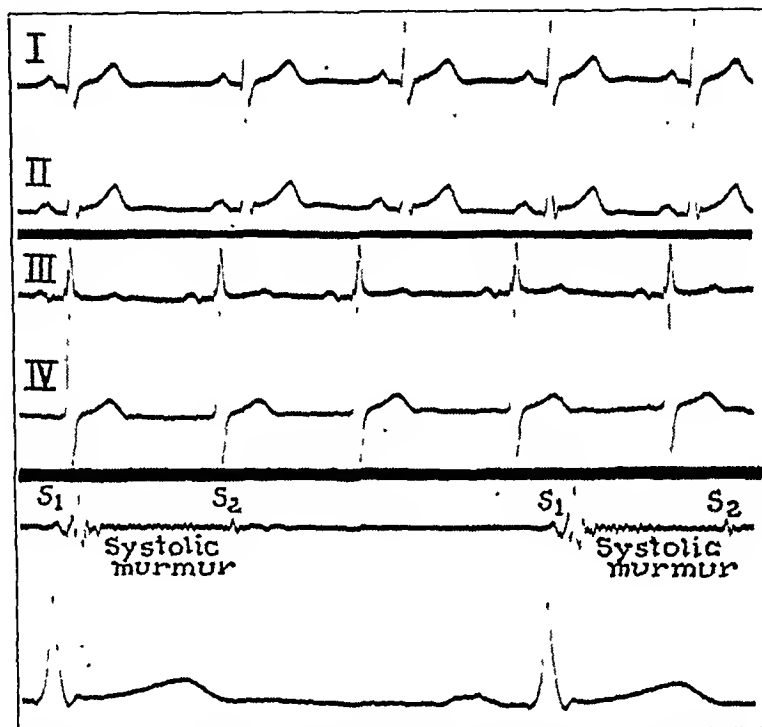


Fig. 1 (case 1).—Chronic cardiac valvular disease, with defect of the mitral valve. The heart was normal in roentgenograms and on fluoroscopy. The electrocardiogram, of which the four conventional leads are shown, is entirely normal, but the phonocardiogram reveals a prolonged murmur throughout the systole.

to the patient's physician as objective proof of an organic lesion, and the young man was advised to abandon the idea of entering the armed forces. The matter was considered closed.

Sometime later, while making rounds on a ward for cardiac patients in a Naval Hospital in the Pacific, I found J. S. A. in bed with heart failure. He had been admitted with advanced pulmonary congestion. On questioning him, I found that he had continued his attempts to enter the navy and had finally been accepted for the Marine Corps. Although he had at first performed his duties without difficulty, his cardiac condition flared up during the invasion of Guam and pulmonary edema ensued. ✕.

It is interesting to note that even during and after development of heart failure the patient's heart was not enlarged. It is generally believed that enlargement of the heart is concomitant with heart failure, but in

early cases enlargement may not be apparent. Perhaps the enlargement is relative and not absolute. This case illustrates the fact that a long (holosystolic) murmur should be accepted as evidence of organic valvular heart disease unless this interpretation can be shown to be untenable.

CASE 2.—W. J. F., a married woman aged 27, was first seen during May 1941. Sudden hemoptysis had developed, followed a few days later by pulmonary edema. Physical examination revealed mitral stenosis; there was a presystolic murmur at the apex, a loud first mitral sound and a loud second pulmonic sound. The past history was noncontributory except that during the last six years she had had an apical systolic murmur which was discovered accidentally. This murmur was considered to be of organic nature by only one of the many physicians whom she had consulted.

The patient had given birth to two children, each of whom survived only a few months. The second child had recently died of Niemann-Pick disease. The mother became prostrated, and the emotional factor had undoubtedly precipitated the acute episode of hemoptysis and pulmonary edema.

A teleroentgenogram showed that the heart was somewhat pendulous and that there was straightening of its left border, that is, the region of the pulmonary artery was prominent. Fluoroscopic examination revealed that the left auricle was enlarged although the left main bronchus was not elevated. Electrocardiographically there was no definite evidence of disease of the valve or of the muscle. The P wave in lead III was inverted.

CASE 3.—W. H., aged 22, was seen in consultation at the United States Naval Hospital, St. Albans, Long Island, on April 4, 1945. A history of chorea at the age of 7 years and of repeated nosebleeds between the ages of 5 and 17 years was given. A systolic thrill was palpable at the apex, and a harsh prolonged systolic murmur was heard in the mitral and apical areas. The first sound was loud, and the pulmonic second was accentuated. The blood pressure was 126 systolic and 86 diastolic. After exercise, a presystolic murmur was heard.

A roentgenogram showed that the heart was not enlarged but that there was prominence in the region of the pulmonary artery. In the left oblique position the left auricle was enlarged; the left main bronchus was not elevated. The electrocardiogram showed no abnormality. The phonocardiogram revealed a prolonged systolic murmur over the mitral area. At the pulmonic and aortic areas the murmurs were not so prolonged.

It is clear that the harsh prolonged systolic murmur was due to defect of the mitral valve.

CASE 4.—R. J. M., a marine aged 25, was seen on June 5, 1945, at the United States Naval Hospital, St. Albans, Long Island. The patient had rheumatic fever at the age of 11 years. When he was at the age of 12, application for insurance was refused. He enlisted in the army in 1940 but was discharged in 1942 with a diagnosis of valvular heart disease. In 1943 he was inducted into the Marine Corps because the recruiting officer could not find evidence of organic heart disease. In May 1945 he complained of dyspnea on exertion and occasional sharp precordial pain.

On examination at St. Albans, a loud, blowing apical systolic murmur was heard, which was "sea-gull" in character; the first sound was snappy and the second pulmonic sound accentuated. The blood pressure was 126 systolic and 68 diastolic. The teleroentgenogram showed that the left border of the heart was

straightened and the right border was increased in convexity (fig. 2A). In the left oblique position the left auricle was enlarged and filled in the space below the left main bronchus (fig. 2B). The electrocardiogram revealed a tendency toward right axis deviation. Even more significantly, the phonocardiogram disclosed a systolic murmur throughout the systole (fig. 4C).

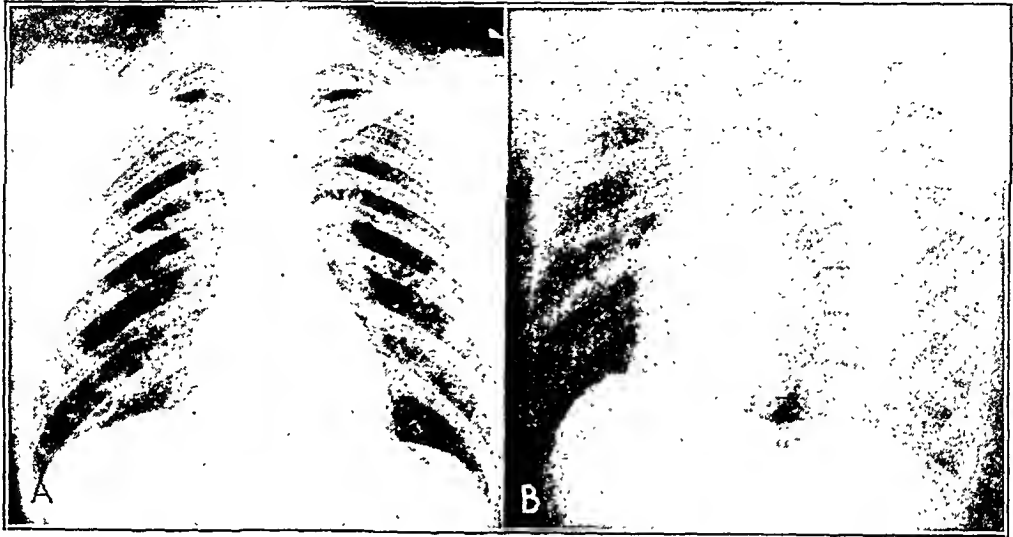


Fig. 2 (case 4).—*A*, chronic rheumatic cardiac valvular disease, with involvement of the mitral valve. The heart is not enlarged, but the right border is convex, and the left border is straight in the region of the pulmonary arc and the left auricular appendage. *B*, in the left oblique position may be seen the enlarging left auricle filling in the space beneath the left main bronchus. The latter, however, is not elevated.

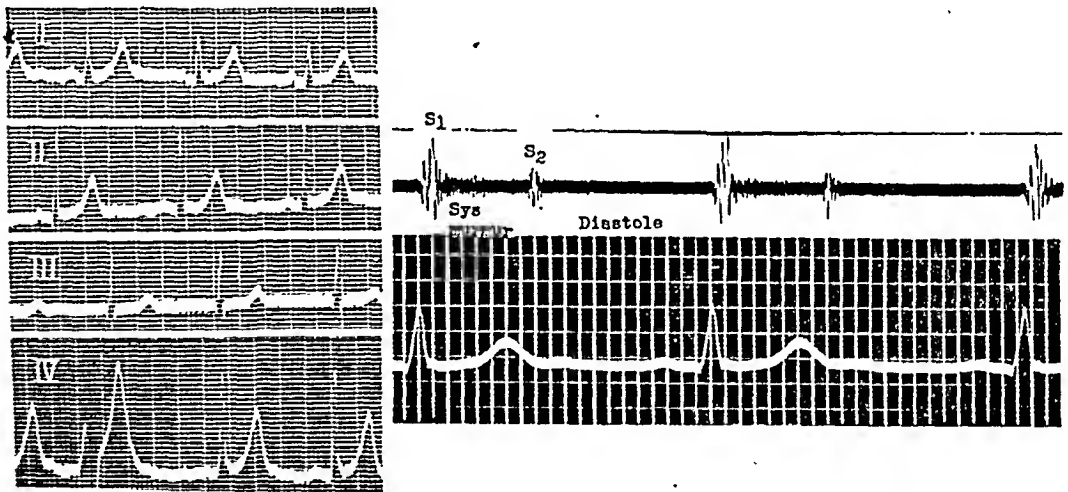


Fig. 3 (case 5).—Chronic rheumatic cardiac valvular disease, with involvement of the mitral valve. The electrocardiogram is normal. The phonocardiogram reveals a high-pitched systolic murmur throughout the systole and a short early diastolic murmur.

The history of rheumatic fever, the "sea-gull" character of the murmur and its prolonged nature on the phonocardiogram, the roentgenographic and fluoroscopic evidence of an enlarged left auricle, and the right axis deviation in the electrocardiogram were proof of the organic nature of the loud apical systolic murmur.

CASE 5.—D. W., aged 21, was admitted in April 1945 to the United States Naval Hospital, St. Albans, Long Island, with rheumatic fever. When he was seen in consultation on May 17, 1945, a prolonged systolic murmur was heard at the apical region. After exercise, this murmur took on a "sea-gull" character. The blood pressure was 140 systolic and 78 diastolic.



Roentgenologic examination showed that the heart was not enlarged; it was globular in shape. In the left oblique position the left auricle was enlarged but the left main bronchus was not elevated. The electrocardiogram was normal (fig. 3), but the phonocardiogram revealed a high-pitched systolic murmur and a short diastolic murmur (fig. 3).

The presence of rheumatic fever, a "sea-gull" quality of the murmur, a globular-shaped heart, left auricular enlargement, and phonocardiographic evidence proved the organic nature of the prolonged apical systolic murmur at the apex.

#### DIAGNOSIS

To determine whether a patient who exhibits a systolic murmur at the apex has organic heart disease, resort must be had to the information provided by the patient's history and by physical and laboratory examination.

*History.*—A record of rheumatic fever for a patient with a loud apical systolic murmur should be accepted as almost certain evidence that a defect of the mitral valve exists. Likewise, the history of an infection by group A. Str. hemolyticus must now be regarded as of similar significance. Many recent articles<sup>9</sup> afford proof of the relationship of this type of infection to rheumatic fever and rheumatic heart disease.

*Physical Examination.*—The value of repeated examination of patients who have a questionable systolic murmur cannot be emphasized too strongly. Frequently the presence of a murmur can be established only after examination in different positions and after exercise, because in cases of early valvular heart disease the murmurs are transient. When I have difficulty in coming to a decision, I routinely examine the patient at least three times.

In the early stages of valvular heart disease the heart is not enlarged, an apex thrill is not usually palpable and diastolic murmur is not routinely audible. The first sound at the apex is loud, as is the second pulmonic sound. The murmur at the apex is loud and prolonged; it begins and is concurrent with the first sound. The presence of "musical" murmur, "sea-gull" murmur, "harsh" murmur or "constant" murmur strengthens the diagnosis. As early as 1832, Hope<sup>10</sup> described the evanescent character of mitral murmurs. The left lateral recumbent position and the sitting position, with the patient leaning forward and to the left, are the most advantageous for examination. Repeated exami-

9. Watson, R. F.: Rothbard, S., and Swift, H. F.: The Relationship of Post-scarlatinal Arthritis and Carditis to Rheumatic Fever, *J.A.M.A.* **128**:1145 (Aug. 18) 1945. Suarez, R. M.: The Incidence of Heart Disease in Puerto Rico: Statistical Analysis of 1,081 Cases, *Am. Heart J.* **29**:339 (March) 1935. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, *Arch. Int. Med.* **76**:131 (Sept.) 1945. Connor, C. A. R.: Experiences with Rheumatic Fever in the Army Air Forces, *Am. J. Pub. Health* **36**:236 (March) 1946.

10. Hope, J.: *A Treatise on the Diseases of the Heart*, London, W. Kidd, 1832.

nations may not only elicit a loud apical systolic murmur which persists for some time but may also disclose the presence of a diastolic murmur, thereby confirming the diagnosis of disease of the mitral valve. A systolic murmur at the apex produced by exercise is not necessarily evidence of organic heart disease. The murmur indicative of heart disease is loud and prolonged and persists for a longer period than is to be expected from the effect of exercise alone. Effort, particularly if strenuous, produces murmurs in a healthy person, but these disappear almost immediately after cessation of exertion and certainly as the heart rate slows. Moreover, such murmurs are not loud. Freeman and Levine<sup>8</sup> found that in healthy persons murmurs of grades 1 and 2 were common after exercise but that grade 3 murmurs did not appear. Friedlander and Brown<sup>11</sup> substantiated this observation.

Inhalation of amyl nitrite has been advocated<sup>12</sup> as a method of bringing out loud, harsh, prolonged, persisting systolic murmurs and of disclosing the presence of a diastolic murmur, particularly a presystolic one. Friedlander and Brown<sup>11</sup> stated that they never heard a "loud" murmur after administration of amyl nitrite to normal persons. An objection to the use of amyl nitrite arises from that fact that it causes distressing headache at times. It should be used only if the patient is unable to exercise.

*Teleoroentgenograms and Fluoroscopy.*—In early disease of the mitral valve, neither teleoroentgenographic nor fluoroscopic study reveals cardiac enlargement, elevation of the left main bronchus, the appearance of a left auricular arc far over the right side of the heart or indentation of the barium-filled esophagus. These abnormalities are revealed only in cases of well established disease of the mitral valve. There are, however, two important diagnostic signs to be observed in beginning involvement of the mitral valve. Fluoroscopic examination in the left oblique position shows the space beneath the left main bronchus filled by the expanding auricle.<sup>13</sup> "Straightening" of the left border of the heart caused by the prominence in the region of the pulmonary artery may also be seen.<sup>14</sup> This bulge, according to Grishman, Sussman and Steinberg,<sup>14</sup> is produced as the enlarging left auricle pushes the pulmonary artery up and to the

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11. Friedlander, R. D., and Brown, M. G.: The Systolic Murmur: Further Observations on Its Clinical Significance, *Ann. Int. Med.* 8:893 (Feb.) 1935.

12. Fahr, G.: The Significance of the Systolic Murmur, *Nebraska M. J.* 15:458 (Dec.) 1930. Friedlander and Brown.<sup>11</sup>

13. Ungerleider, H. E., and Gubner, R.: Roentgenology of the Heart and Great Vessels, in Stroud, W. D.: *Diagnosis and Treatment of Cardiovascular Disease*, ed. 3, Philadelphia, F. A. Davis Company, 1945, p. 789. Master.<sup>1a</sup>

14. Grishman, A.; Sussman, M. L., and Steinberg, M. F.: Angiocardiographic Analysis of the Cardiac Configuration in Rheumatic Mitral Disease, *Am. J. Roentgenol.* 51:33 (Jan.) 1944.

left. Fineberg and Steuer<sup>15</sup> and also Wolfson<sup>16</sup> stress the help to be obtained from the roentgenogram.

*Phonocardiogram.*—The phonocardiogram is a useful adjunct in establishing the presence of disease of the mitral valve.<sup>17</sup> When the length of a murmur cannot be accurately determined, this sound-recording apparatus may reveal that the systolic murmur is a long one, occurring throughout the entire systole, that is, "holosystolic." Furthermore, the stethograph may demonstrate the presence of an otherwise inaudible diastolic murmur.

It is not necessary that every practitioner should own or routinely use a heart sound machine, but resort to a recording apparatus may be helpful in the type of case under discussion.

Bass and his colleagues,<sup>18</sup> from a study of systolic murmurs in children, reported that the murmurs heard in cases of organic lesions disclosed low frequency as well as high frequency components whereas functional murmurs exhibited only high frequency vibrations.

*Electrocardiogram.*—On occasion the electrocardiogram may be of value in diagnosing beginning defect of the mitral valve. Right axis deviation of the QRS complex, a P wave of more than 2.5 mm. in height or at least 0.10 second in time or a distinctly notched wave are signs of deformity of the mitral valve.<sup>19</sup> Enlargement of the right side of the heart produces right axis deviation of the QRS waves. The abnormalities of the P wave are due to enlargement of the left auricle or to a change in its position or shape or to a combination of these factors.

#### DIFFERENTIAL DIAGNOSIS

Neurocirculatory asthenia, or effort syndrome or "small heart syndrome,"<sup>20</sup> must be considered in the differential diagnosis of disease of the mitral valve. In neurocirculatory asthenia a systolic thrill may be palpated and a loud apical systolic murmur may be heard on auscultation concomitantly with a loud first sound at the apex and a loud second

15. Fineberg, M. H., and Steuer, L. G.: Apical Systolic Murmurs in Children: Follow-Up Observations in One Hundred Cases, *Am. Heart J.* 7:553 (June) 1932.

16. Wolfson, I. N.: Clinical and Laboratory Studies of Ninety-One Workers with Apical Systolic Murmurs, *New England J. Med.* 233:757 (Dec. 20) 1945.

17. Bartlett, W. M.: Combined Electrocardiography, Stethography and Cardioscopy in the Selection of Pilots, *J. Aviation Med.* 12:2 (March) 1941.

18. Bass, M.; Mond, H.; Messeloff, C., and Oppenheimer, E.: The Systolic Murmurs in Children, *J.A.M.A.* 101:17 (July 1) 1933.

19. (a) Berliner, K., and Master, A. M.: Mitral Stenosis: A Correlation of Electrocardiographic and Pathologic Observations, *Arch. Int. Med.* 61:39 (Jan.) 1938. (b) Master, A. M.: The Electrocardiogram and X-ray Configuration of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942, p. 148. (c) White, B. V.; Parker, R. C., Jr., and Master, A. M.: Disease of the Mitral Valve: Its Effect on the Pattern of the Electrocardiogram, *Arch. Int. Med.* 74:94 (Aug.) 1944.

20. Master, A. M.: Neurocirculatory Asthenia Due to Small Heart, *M. Clin. North America* 28:577 (May) 1944.

pulmonic sound. To add to the difficulty of differentiation, the roentgenogram demonstrates a straight left border of the heart and the electrocardiogram may disclose the abnormalities previously described for disease of the mitral valve.<sup>21</sup> The differentiation can usually be made on the basis of other, well recognized symptoms of neurocirculatory asthenia. The patient is nervous, reveals a tremor and complains of dizziness and giddiness and often of severe precordial pain unrelated to effort. Symp-

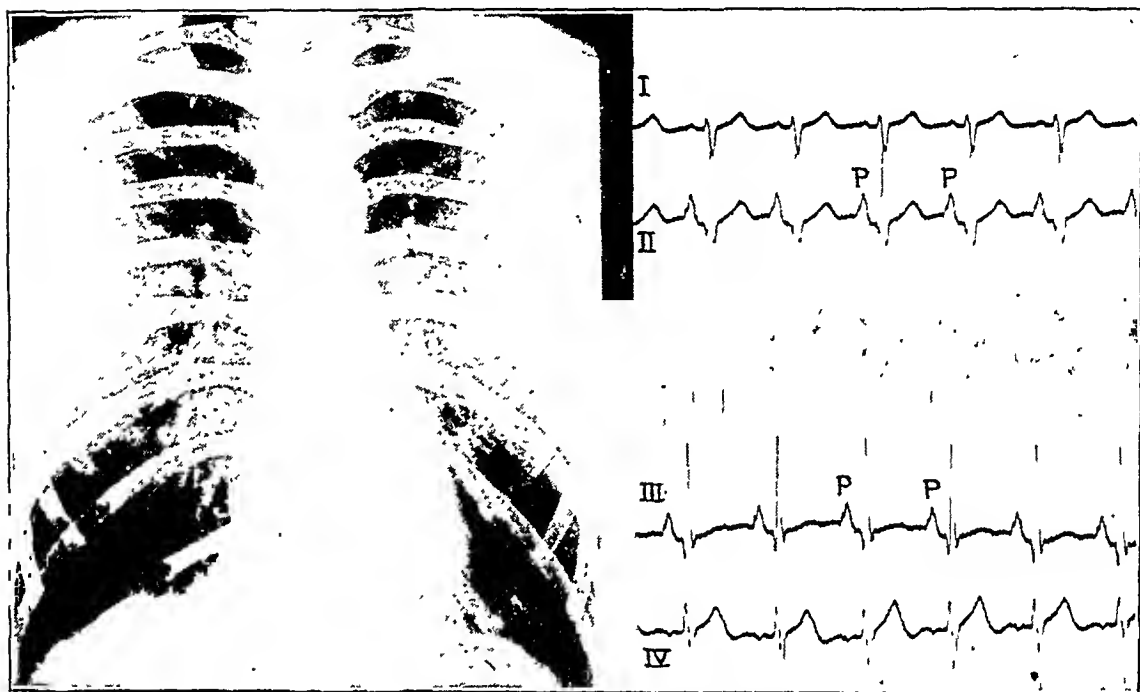


Fig. 4 (case 6).—Effort syndrome (small heart syndrome, or neurocirculatory asthenia). The diaphragm is in a low position, with a long, pendulous, narrow heart. The electrocardiogram reveals right axis deviation of the QRS waves, low amplitude in lead I and relatively large amplitude in leads II and III. The P (auricular) waves are large.

toms of an anxiety neurosis are also present. Moreover, neurocirculatory asthenia almost always appears in long thin persons having low diaphragms and long, narrow or small hearts. The following history is characteristic of this type of patient.

CASE 6.—H. T. H., aged 31, was seen at the National Naval Medical Center on Jan. 30, 1943. His weight was 120 pounds (54 Kg.) and his height 5 feet 10 inches (178 cm.). The past history was noncontributory. He was referred to the center because of a questionable systolic murmur. An electrocardiogram had disclosed right axis deviation, with large P waves. On examination a blowing systolic murmur was heard at the apex. A teleoroentgenogram showed that the diaphragm was low in position and that the heart was narrow and pendulous (fig. 4).

An electrocardiogram revealed right axis deviation of the QRS complex and low amplitude in lead I, with relatively high amplitudes in leads II and III. The P waves were tall (fig. 4). The diagnosis of neurocirculatory asthenia was made because the man was tall and thin and because the roentgenogram revealed a low diaphragm and a narrow pendulous small heart.

21. Master (footnotes 1a, 19b and 20).

*Deformity of the Chest.*—A funnel-shaped chest or merely a thin, flat chest may give rise to signs of mitral valve disease.<sup>22</sup> Not only does a person of this bodily formation exhibit harsh apical systolic murmur but the heart often appears to be enlarged and the left border straightened. Careful examination permits differentiation from disease of the mitral valve. Viewed in an oblique or a lateral position by means of the fluoroscope or in roentgenograms the sunken sternum and the narrow space between the breast bone and the vertebral column become apparent. In these deformities the heart is pushed and rotated into the left side of the

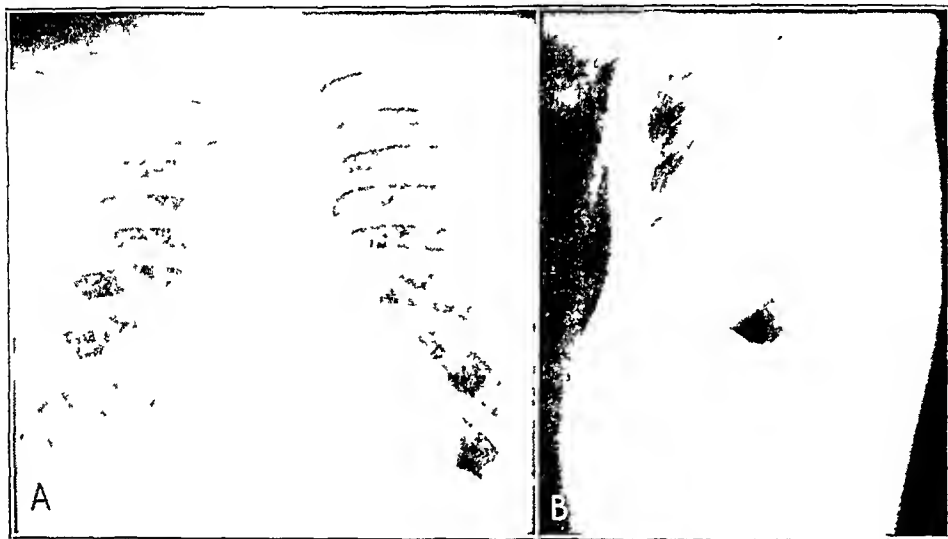


Fig. 5 (case 7).—*A*, funnel-shaped chest. In the teleroentgenogram the heart is seen to be entirely on the left side. The right border is hidden behind the vertebral column, and the left border is straight. *B*, the left lateral view shows the depressed sternum producing the small anteroposterior diameter of the heart.

chest. The spinal column appears to be the right border of the heart, and since the left border is displaced to the left the heart appears to be large but really is not. The next case is an example of this type of deformity.

CASE 7.—W. H. M., a marine aged 19, weighed 195 pounds (88.5 Kg.), and was 6 feet (183 cm.) tall. Pain in the chest and shortness of breath developed during the invasion of Saipan. On examination a systolic murmur was heard at the apex, but a pronounced depression was found at the lower end of the sternum. The electrocardiogram revealed abnormal P waves.

The teleroentgenogram disclosed that the heart was displaced to the left (fig. 5*A*). A lateral view and a fluoroscopic examination showed marked diminution in the anterior-posterior diameter of the heart (fig. 5*B*).

The vital capacity was 3,600 cc, a figure that is low for a person of this size.

The definite depression of the lower part of the chest and the disclosure by lateral view roentgenograms and also by fluoroscopy of an extremely narrow anterior-posterior diameter established the diagnosis of funnel-shaped chest.

22. Master,<sup>10b</sup> p. 349.

*Kyphoscoliosis.*—Like deformity of the chest, kyphoscoliosis may enter into the problem of differentiation.<sup>22</sup> When the scoliosis is toward the right in the dorsal region, the heart is displaced to the left, the left border appears straightened, that is, "mitralized," and the heart itself seems to be enlarged. The enlargement is, however, only apparent: actually the right edge of the dorsal vertebræ is mistaken for the right border of the heart. As with a funnel-shaped or a flat chest, a loud apical systolic murmur is heard and much the same electrocardiographic changes are observed.

*A Split First Sound.*—A split first sound occasionally simulates systolic murmur, and at times it may even resemble the presystolic murmur which arises from deformity of the mitral valve. Careful timing of the sounds and especially a phonocardiographic tracing permit a correct diagnosis<sup>1a</sup> to be made. Both sounds occur early in systole, and they have the relatively large amplitude of heart sounds rather than the smaller amplitude of murmurs. They are practically equal in height and do not appear in diastole.

*Hypertension.*—In hypertension a prolonged apical systolic murmur is not infrequently heard. The patients have high blood pressure of long standing, enlargement of the heart and elongated tortuous dense aorta.<sup>23</sup> Usually they are middle-aged or old and present evidence of generalized arteriosclerosis.

*Hyperthyroidism.*—In hyperthyroidism an apical systolic murmur may be heard, but the characteristic signs and symptoms of this disease distinguish it from rheumatic heart disease.<sup>24</sup> An increased heart rate and an elevated basal metabolic rate point to exophthalmic goiter. Occasionally the two diseases are found in the same person, and many investigators are of the opinion that the milieu of hyperthyroidism provides fertile soil for rheumatic heart disease.<sup>25</sup>

*Anemia.*—Anemia, primary or secondary (not uncommonly the latter), gives rise to loud systolic murmurs heard best at the apex on auscultation. The blood count is, of course, the feature that distinguishes anemia from disease of the mitral valve. Theoretically, secondary anemia occurring in conjunction with rheumatic fever or rheumatic heart disease might create difficulty in differential diagnosis; actually, the valvular defect is obvious.

*Respiratory Murmurs.*—The question of respiratory murmurs frequently enters into the differential diagnosis, though usually not to an

23. Master,<sup>10b</sup> p. 114.

24. Master,<sup>10b</sup> p. 276.

25. Maher, C. C.; Sanders, A.; Plice, S. G., and Wosika, P. H.: A Syndrome of Exophthalmic Goiter, Acute Rheumatic Carditis and Heart Block, *Am. Heart J.* 17:742 (June) 1939.

important degree. Thayer<sup>26</sup> in 1925 pointed out that respiratory murmurs are accentuated during inspiration and usually disappear at some stage of respiration, generally when a full breath is maintained. Sodeman<sup>27</sup> noted that if the patient stops breathing at the end of a full inspiration or expiration or even at any point in the cycle the murmur disappears. As a matter of fact, holding the breath at any phase in breathing generally causes a respiratory murmur to vanish.

#### COMMENT

A loud systolic murmur at the apex should be considered organic in nature until it can be proved to be of other origin. The patients should be treated accordingly even when evidence of past rheumatic fever, enlargement of the heart, diastolic murmur, abnormal electrocardiogram, or heart failure is lacking.\* Such patients should receive antibiotics during various manipulations and diseases which injure the mucous membrane and facilitate the entrance of bacteria into the blood stream which may lead to bacterial endocarditis. The diseases include infections in the ear, nose and throat and genitourinary system and the procedures include operations on the ear, nose and throat and genitourinary system.

A history of rheumatic fever or evidence of infection by group A *Str. hemolyticus* affords confirmatory evidence of the organic origin of a loud apical systolic murmur, but in 20 to 25 per cent of patients, or perhaps in a larger percentage, such evidence is not found. Some years ago Scott<sup>28</sup> and Hedley<sup>29</sup> pointed this out. Recently Flaxman<sup>30</sup> reported that among men rejected for the army in World War II because of systolic murmur of organic valvular origin only 48 per cent gave a history of previous rheumatic fever. Levy, Stroud and White<sup>4</sup> reported even a lower figure, i.e., 28.8 per cent.

That apical systolic murmurs be properly interpreted is of first importance because correct diagnosis may depend on correct evaluation of these murmurs. It should be kept in mind constantly that the sound of these murmurs varies; they may be loud in one examination and not audible in the next, and they vary with alteration in the position of the

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26. Thayer, W. S.: Reflections on the Interpretation of Systolic Cardiac Murmurs, *Am. J. M. Sc.* **169**:313 (March) 1925.

27. Sodeman, W. A.: The Systolic Murmur, *Am. J. M. Sc.* **208**:106 (July) 1944.

28. Scott, R. W.: The Significance of the Systolic Murmur, abstracted, *Proc. Life Insur. M. Dir. America* **21**:114, 1934.

29. Hedley, O. F.: Studies of Heart Disease Mortality: An Analysis of the Accuracy of Deaths Recorded as Being Due to Heart Disease in Washington, D. C., During 1932, with a Discussion of the Defects of the Present Method of Tabulating Deaths, and Suggestions for a New System Based upon Etiological Factors, Bulletin 231, United States Treasury Department, Public Health Service, 1936.

30. Flaxman, N.: Initial Cardiac Examination of Twenty-Three Thousand Inductees and Volunteers, *Am. J. M. Sc.* **209**:657 (May) 1945.

patient. They may disappear for weeks, months or years and then reappear. They may vanish permanently. Coombs<sup>31</sup> reported that in 31 per cent of cases the symptoms of rheumatic heart disease regressed. Bland, Jones and White<sup>32</sup> in a follow-up study of 1,000 patients with valvular disease observed that physical signs became less apparent in a considerable number and that in 83 cases all physical signs vanished permanently. Wilson<sup>33</sup> made similar discoveries. I have observed a man 31 years old who had rheumatic fever and large pericardial effusion. Later there was definite evidence of mitral and aortic disease, with enlargement of the heart. Nevertheless the patient was completely free of all signs at the end of three years. Many cardiologists have encountered similar instances. Swift<sup>34</sup> expressed the opinion that rheumatic valvulitis may clear up entirely in much the same way that the swollen ankle heals in rheumatic fever. Wilson<sup>33</sup> stated the belief that minimal scarring of the valve remains. Her opinion is probably correct, because post-mortem examination frequently discloses evidence of old rheumatic heart disease that was not suspected during life or at least during the last years of life. As early as 1832 Hope<sup>10</sup> noted absence of any murmur even in "tight" mitral stenosis; Flaxman<sup>35</sup> observed this recently. In fact, White<sup>36</sup> stated that in half of the cases of mitral stenosis the disease would remain undiagnosed if the diagnosis were based solely on the presence of presystolic murmur.

In the evaluation of apical systolic murmurs, the loudness or the intensity of the murmur is of more significance than its transmission. As Levine and Likoff<sup>37</sup> showed, the louder the murmur the greater the transmission. Scott,<sup>28</sup> Levine,<sup>38</sup> Sodeman<sup>27</sup> and Shapiro<sup>39</sup> expressed the belief that the importance of a murmur increases with its loudness.

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31. Coombs, C. F.: *Rheumatic Heart Disease*, New York, William Wood & Company, 1924.

32. Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of the Physical Signs of Rheumatic Heart Disease, *J.A.M.A.* **107**:569 (Aug. 22) 1936.

33. Wilson, May G.: *Rheumatic Fever: Studies of the Epidemiology, Manifestations, Diagnosis, and Treatment of the Disease During the First Three Decades*, New York, The Commonwealth Fund, 1940, p. 393.

34. Swift, H.: Personal communication to the author.

35. Flaxman, N.: Historical Aspects of Mitral Stenosis, *M. Rev. of Rev.* **42**:461 (Nov.) 1936.

36. White, P. D.: *Heart Disease*, ed. 3, New York, The Macmillan Company, 1944, p. 81.

37. Levine, S. A., and Likoff, W. B.: Some Notes on the Transmission of Heart Murmurs, *Ann. Int. Med.* **21**:298 (Aug.) 1944.

38. Levine, S. A.: The Systolic Murmur: Its Clinical Significance, *J.A.M.A.* **101**:436 (Aug. 5) 1933.

39. Shapiro, M. J.: Follow-Up Study of Systolic Murmurs, *Am. Heart J.* **17**:416 (April) 1939.



White,<sup>40</sup> in a report on the clinical significance of apical heart murmurs in 1,000 patients, stated that loud murmurs were almost always an indication of an abnormal heart. It is of interest that in the aged, too, loud apical systolic murmurs have been found to signify organic heart disease.<sup>7</sup>

#### SUMMARY

Experience during the recent war brought into prominence the consequences of failure to recognize apical systolic murmur as an indication of organic disease of the mitral valve. Army and Navy personnel with such murmurs had to be reexamined frequently, lost valuable time in hospitals, were a burden to the government and a source of additional expense. Finally, in certain instances, heart failure developed under the mental and physical exigencies of war.

Similarly, in civilian life cardiovascular complaints and even heart failure may be precipitated by emotional stress, physical exertion, recurrence of rheumatic fever or infection with group A Str. hemolyticus.

For adequate protection of patients, loud systolic murmurs at the apex unaccompanied with a systolic thrill, an enlarged heart, diastolic murmur, an abnormal electrocardiogram and evidence of heart failure should be most carefully appraised. According to insurance statistics, the mortality rate for persons with this murmur is increased. Hard physical work may shorten the span of life.

Defect of the mitral valve or even subacute bacterial endocarditis may suddenly become apparent in persons in whom the only sign of organic valvular disease has been the presence for years of apical systolic murmur.

Seven cases are cited to illustrate the diagnostic criteria required to appraise the significance of apical systolic murmur.

A history of rheumatic fever or of infection with group A Str. hemolyticus given by a patient with a loud apical systolic murmur should be accepted as almost certain evidence of defect of the mitral valve.

The diagnostic signs to be sought in physical examination are a loud first apical and a loud second pulmonic sound. A prolonged murmur is significant. A "musical," "sea-gull," "harsh" or "constant" murmur tends to confirm the presence of organic heart disease.

Patients should be examined repeatedly, in different positions and after exercise, since the murmurs of early valvular heart disease are transient. Such careful investigation may disclose not only a loud systolic murmur but also a diastolic murmur. It is only in cases of advanced heart disease that one finds a distinct systolic thrill, enlargement of the heart, diastolic murmurs, abnormal electrocardiograms and signs of heart failure.

Murmurs following exertion are significant only when they are loud and prolonged and persist after the heart rate has slowed. Inhalation of amyl nitrite may serve to elicit heart sounds if a patient is unable to exercise.

40. White, P. D.: The Clinical Significance of Apical Heart Murmurs, *Am. J. M. Sc.* 174:732 (Dec.) 1927.

Two signs of beginning mitral valve deformity are to be seen in roentgenograms and on fluoroscopic examination. In the left oblique position the space beneath the left main bronchus is filled by the enlarging left auricle. In the posterior-anterior view the left border of the heart may be "straight," a result of prominence in the region of the pulmonary artery. Only in long established disease of the mitral valve does one find cardiac enlargement, elevation of the left main bronchus produced by the large left auricle, a left auricular arc far over on the right side of the heart or indentation of the barium-filled esophagus.

The phonocardiogram may prove helpful in establishing the duration of a systolic murmur and may demonstrate an otherwise inaudible diastolic murmur. The electrocardiogram is most helpful in the diagnosis of advanced involvement of the mitral valve, but occasionally when there is early impairment it reveals abnormal P (auricular) waves and right axis deviation.

Neurocirculatory asthenia frequently offers a problem in differential diagnosis. However, patients with this disease commonly present symptoms of anxiety neurosis. In addition, they are usually of the asthenic type, with a low diaphragm and a long, narrow, small heart.

Funnel and flat-shaped chests and kyphoscoliosis involving the right dorsal area often cause symptoms which simulate those of rheumatic involvement of the mitral valve. Mere inspection of the chest, roentgenograms and fluoroscopic examination demonstrate the deformity. Occasionally a split first sound is mistaken for a systolic murmur. Its occurrence in early systole distinguishes it from the latter.

Hypertension, hyperthyroidism and anemia can produce loud apical systolic murmurs. The diagnostic characteristics of these illnesses demarcate them from disease of the mitral valve.

The respiratory murmur is characterized by its relation to breathing and its disappearance when the breath is held.

There may be organic disease of the mitral valve without a history of rheumatic fever. The physical signs of rheumatic heart disease may regress. These developments make it harder to evaluate the significance of apical systolic murmurs, but a knowledge of all the difficulties, including these and others previously described, is a necessary step in their solution.

Establishment of the organic nature of a murmur does not afford a criterion of the heart's function. Patients may be able to live a normal life to a ripe old age. Unsuspected rheumatic disease of the mitral valve not infrequently is first discovered in old age or even at autopsy.

The loudness of a systolic murmur is of more diagnostic value than its transmission. The latter depends on the intensity of the murmur. A loud apical systolic murmur should be accepted as evidence of organic mitral valve disease until this is disproved. A "loud" murmur is not heard in normal hearts of either young or old.

# Progress in Internal Medicine

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## GASTROENTEROLOGY

A Review of the Literature from July 1946 to July 1947

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CHICAGO

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago School of Medicine.

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## INTRODUCTION

As in preceding years, this review does not include the liver, gall-bladder, biliary tract or pancreas. Nevertheless the size of the task is indicated by the fact that the present review is based on an analysis of more than six hundred articles. Every effort has been made to incorporate all worth while contributions, but the reviewers recognize the possibility that some valuable papers may have been unintentionally overlooked.

The gastroenterologic literature for the past year consists chiefly of interesting and useful clinical observations, statistical analyses and case studies. The variety and the volume of the recorded clinical material are truly impressive. Nearly one fifth of the review is composed of articles on peptic ulcer. Many of the reports deal with advances in surgical technic. There has been a relative scarcity of papers devoted primarily to research, approximately 20 per cent; indeed, only a small percentage of these deal with basic problems in gastroenterology.

## BOOKS

Numerous texts on various phases of gastroenterology<sup>1</sup> have been published during this period. Because of the length of the review, it has seemed advisable to comment briefly on only a few of these. Many of the foreign books have not been available to the reviewers. Turner<sup>1a</sup> discusses informally his extensive experience with injuries and diseases of the esophagus. The second edition of "Human Gastric Function" by Wolf and Wolff<sup>1d</sup> maintains the high quality of the first edition of this competent and significant study of gastric physiology. Schindler<sup>1c</sup> has comprehensively analyzed his twenty-five years' experience with gastritis

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1. (a) Turner, G. G.: *Injuries and Diseases of the Esophagus*, London, Cassel & Co., 1947. (b) Collett, F. J.: *Les troubles de l'innervation pharyngolaryngée et esophagienne*, Paris, Masson & Cie, 1946. (c) Buchs, S.: *Die Biologie des Magenkathepsins: Experimentelle Untersuchungen zur Physiologie und Fermentchemie der Eiweissverdauung in Magen*, Basel, S. Karger, 1947. (d) Wolf, S., and Wolff, H. G.: *Human Gastric Function: An Experimental Study of a Man and His Stomach*, New York, Oxford University Press, 1947. (c)

in a book which should interest all students of the subject. Ulcer of the stomach, duodenum and jejunum is clearly portrayed by Brown.<sup>1f</sup> "The Radiologic Examination of the Small Intestine" by Golden,<sup>1j</sup> the second edition of Wangenstein's "Intestinal Obstruction"<sup>1i</sup> and the ninth edition of Cope's "The Early Diagnosis of the Acute Abdomen"<sup>1o</sup> are valuable books by outstanding authorities. Brunschwig<sup>1s</sup> presents a detailed and interesting analysis of the results of radical surgical intervention in 100 unselected patients with advanced abdominal cancer. Other American texts include Fradkin's<sup>1p</sup> "Diagnosis and Treatment of Diarrheal Diseases," Spiesman's<sup>1q</sup> "Essentials of Clinical Proctology" and Pelter's<sup>1k</sup> "Gastroenterology in General Practice."

### ESOPHAGUS

*General.*—Howard<sup>2</sup> discusses the value of esophagoscopy and recommends its more frequent application by gastroenterologists.

*Esophagogastroscope.*—A new type of esophagoscope has been developed by Boros.<sup>3</sup> The outstanding feature of the instrument is the softness and extreme mobility of its tip, facilitating passage beyond the pharynx into the esophagus and even into the stomach without the attendant dangers of the rigid, unyielding instrument.

*Congenital Atresia.*—The roentgen features of congenital atresia of the esophagus in 45 consecutive patients with this anomaly are described,

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Schindler, R.: Gastritis, New York, Grune & Stratton, Inc., 1947. (f) Brown, R. C.: Ulcer of the Stomach, Duodenum and Jejunum, New York, Oxford University Press, 1946. (g) Nasio, J.: Tratamiento medico de la ulcera gastroduodenal experimental, Buenos Aires, La prensa medica argentina, 1946. (h) Laureys, S.: Pathogenie de l'ulcere rond, cancer, syphilis et autres maladies, Antwerp, the Author, 1946. (i) Maingot, R.: Technique of Gastric Operation, London, Oxford University Press, 1946. (j) Golden, R.: Radiologic Examination of the Small Intestine, Philadelphia, J. B. Lippincott Company, 1946. (k) Pelter, L., and Held, L. A.: Gastroenterology in General Practice, Springfield, Ill., Charles C Thomas, Publisher, 1947. (l) Wangenstein, O. H.: Intestinal Obstructions, ed. 2, *ibid.*, 1947. (m) McNeill, R. J.: The Appendix, London, H. K. Lewis & Co., Ltd., 1946. (n) Short, A. R.: The Causation of Appendicitis, Bristol, John Wright & Sons, Ltd., 1946. (o) Cope, Z.: The Early Diagnosis of the Acute Abdomen, ed. 9, New York, Oxford University Press, 1946. (p) Fradkin, W. Z.: The Diagnosis and Treatment of Diarrheal Diseases, New York, Grune & Stratton, Inc., 1947. (q) Spiesman, M. G.: Essentials of Clinical Proctology, *ibid.*, 1947. (r) d'Allaines, F.; LeRoy, A., and Dubost, C.: Traitement chirurgical du cancer du rectum, Paris, Ernest Flammarion, 1946. (s) Brunschwig, A.: Radical Surgery in Advanced Abdominal Cancer, Chicago, University of Chicago Press, 1947. (t) Cameron, T. W. M.: The Parasites of Man in Temperate Climates, Toronto, Canada, University of Toronto Press, 1947.

2. Howard, J. T.: Adventures in the Esophagus, *South. M. J.* **40**:197-206, 1947.

3. Boros, E.: Esophagoscopy by Means of a Flexible Instrument: A New Esophago-Gastroscope, *Gastroenterology* **8**:724-728, 1947.

42 of whom also had tracheoesophageal fistula.<sup>4</sup> Congenital partial atresia of the esophagus associated with congenital diverticulum of the esophagus<sup>5</sup> and a case of congenital atresia of the esophagus in which a segment of the esophagus was absent, both sections ending blindly in the thorax, also are recorded.<sup>6</sup> Ladd and Swenson<sup>7</sup> describe the surgical technic for the treatment of esophageal atresia and tracheoesophageal fistula, utilizing a retropleural approach through the right thoracic region of the back; the operation was successful in 30 of 76 babies. A patient with complete atresia of the esophagus and tracheoesophageal fistula was operated on successfully by means of an end to end anastomosis.<sup>8</sup>

*Spontaneous Rupture.*—Three consecutive cases of fatal spontaneous rupture of the esophagus were observed by Eliason and Welty<sup>9</sup> in one year; in the patient described by Frink<sup>10</sup> recovery occurred without operation.

*Perforation.*—Perforation of the esophagus by a foreign body, producing a putrid pulmonary abscess,<sup>11</sup> and penetration of the esophagus by a small bone eroding into the aorta<sup>12</sup> are described. Retropharyngeal perforation of the esophagus occurred during gastroscopy after considerable manipulation of the instrument.<sup>13</sup>

*Foreign Bodies.*—A frequently observed roentgen sign of foreign bodies in the esophagus, according to Johnstone,<sup>14</sup> is the presence, on swallowing, of a bolus of air in the segment containing the foreign body. The only other condition which may produce a similar appearance is an

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4. Holt, J. F.; Haight, C., and Hodges, F. J.: Congenital Atresia of the Esophagus and Tracheo-Esophageal Fistula, *Radiology* **47**:457-470, 1946.

5. O'Bannon, R. P.: Congenital Partial Atresia of the Esophagus Associated with Congenital Diverticulum of the Esophagus, *Radiology* **47**:471-477, 1946.

6. Davis, M. M.: Congenital Atresia of the Esophagus, *Canad. M. A. J.* **56**:539-541, 1947.

7. Ladd, W. E., and Swenson, O.: Esophageal Atresia and Tracheo-Esophageal Fistula, *Ann. Surg.* **125**:23-40, 1947.

8. White, M. L., Jr., and Birdsong, M.: Congenital Esophageal Atresia with Tracheo-Esophageal Fistula, *Surgery* **20**:548-557, 1946.

9. Eliason, E. L., and Welty, R. F.: Spontaneous Rupture of the Esophagus, *Surg., Gynec. & Obst.* **83**:234-238, 1946.

10. Frink, N. W.: Spontaneous Rupture of the Esophagus: Report of a Case with Recovery, *J. Thoracic Surg.* **16**:291-297, 1947.

11. Hennell, H.: Perforation of Esophageal Foreign Body into Lung: Putrid Pulmonary Abscess; Case Report, *J. Mt. Sinai Hosp.* **13**:203-204, 1946.

12. Lascano, E. F., and Señorans, A. J.: Fistula esofagico—aortica infeccioso, consecutiva a ura herida esofagico por cuerpo extraño, *Arch. agent. de enferm. d. ap. digest. y de la nutrición* **21**:209-217, 1946.

13. Paül, W. D., and Antes, E. H.: Perforation of the Esophagus Caused by Flexible Gastroscope, *Rev. Gastroenterol.* **13**:23-25, 1946.

14. Johnstone, A. S.: Foreign Bodies in the Esophagus, *Brit. J. Radiol.* **20**:41-42, 1947.

abscess in the paraesophageal tissues, usually differentiated by the presence of a fluid level.

*Stricture.*—Three patients with benign strictures of the esophagus were treated successfully by esophagectomy and esophagogastric anastomosis performed in one stage.<sup>15</sup>

*Diverticula.*—Janes<sup>16</sup> describes 6 cases of pulsion diverticula of the lower part of the esophagus; the patients, 5 men and 1 woman, were from 41 to 59 years of age. The chief symptoms were dysphagia, pain, vomiting and loss of weight.

*Cardiospasm.*—The most effective method of treatment of cardiospasm, according to Vinson,<sup>17</sup> consists in stretching the cardia by means of large esophageal sounds or a hydrostatic dilator passed over a previously swallowed silk thread. Patients who have slight dilatation above the point of obstruction and in whom severe pain is a prominent symptom are more resistant to treatment than those with marked dilatation and angulation of the esophagus. Grimson and others<sup>18</sup> found a definite change in the size of the esophagus after cardioplasty in 8 of 9 cases; in 4 the esophagus gradually decreased to normal seven, thirty-four, thirty-seven and fifty-three months respectively after operation, in 2 it was almost normal at three and eleven months and in 2 it was significantly reduced in size at ten days and three months. One patient obtained no relief of obstruction, and there was no decrease in the size of the esophagus. Satisfactory results in the treatment of cardiospasm by esophagogastrostomy are reported also by Bell<sup>19</sup> in 8 of 10 cases; 2 patients required a subsequent operation. Schiebel<sup>20</sup> records good results in 4 cases of cardiospasm similarly treated and observed for six to thirty-five months. The experience of the reviewers is in accord with the observations of Vinson that the vast majority of patients with cardiospasm are completely relieved by mechanical dilation of the cardia and that surgical intervention is required for only a few.

*Peptic Ulcer.*—Morton and Brunschwig<sup>21</sup> report an instructive case in which peptic ulcer of the esophagus was present in a 65 year old wom-

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15. Sweet, R. H.: Subtotal Esophagectomy with High Intrathoracic Esophagogastric Anastomosis in the Treatment of Extensive Cicatricial Obliteration of the Esophagus, *Surg., Gynec. & Obst.* **83**:417-427, 1946.

16. Janes, R. M.: Diverticula of the Lower Thoracic Esophagus, *Ann. Surg.* **124**:637-652, 1946.

17. Vinson, P. P.: Diagnosis and Treatment of Cardiospasm, *South. M. J.* **40**:387-392, 1947.

18. Grimson, K. S.; Reeves, R. J.; Trent, J. C., and Wilson, A. D.: The Treatment of Patients with Achalasia by Esophagogastrostomy, *Surgery* **20**:90-95, 1946.

19. Bell, G. G.: The Treatment of Cardiospasm by Esophagogastrostomy, *Surgery* **20**:104-116, 1946.

20. Schiebel H. M.: Treatment of Esophageal Achalasia or Cardiospasm, *Surgery* **20**:558-570, 1946.

21. Morton, D. R., and Brunschwig, A.: Peptic Ulcer of the Esophagus: Report of a Patient with Ten Year Follow-Up, *Gastroenterology* **7**:314-319, 1946.



an observed for a period of ten years. The original symptoms consisted of postprandial epigastric burning relieved by alkalis and a bland diet, vomiting associated with substernal pain, increasing dysphagia and a loss of weight of 45 pounds (25 Kg.). Roentgen study revealed a 3 to 4 mm. irregular narrowing of the esophagus at the level of the seventh thoracic vertebra; the diameter was 3 to 4 mm. in the 10 cm. involved. The narrowing was not affected by inhalation of amyl nitrite. Esophagoscopy demonstrated a narrowing in the midportion of the esophagus and a well demarcated ulcer on the right lateral wall surrounded by a granular friable mucosa. Three biopsies revealed chronic ulceration. Gastrostomy utilizing a Pezzer catheter was performed, after which the patient gained weight and strength. She returned ten years later because of episodes of vomiting of blood for the preceding five months. Roentgen studies revealed the same constriction in the esophagus, somewhat less irregular, and a crater 3 mm. in diameter in the duodenal bulb. Esophagoscopy demonstrated a fibrous constriction at the site of the old lesion, which prevented passage of the instrument; however a no. 20 bougie was passed with little resistance. Feedings of milk and cream were given through the gastrostomy opening. The patient improved rapidly and was discharged in good condition.

*Cardioesophageal Relaxation.*—Cardioesophageal relaxation, according to Neuhauser and Berenberg,<sup>22</sup> is an infrequent but important cause of vomiting in the newborn. The diagnosis is suggested by the observation of persistent regurgitation which is alleviated by placing the patient in the erect position. Fluoroscopic examination demonstrates retrograde filling of the esophagus during inspiration or increase in intra-abdominal pressure, with persistent relaxation of the esophageal hiatus.

*Scleroderma.*—In a carefully studied case of scleroderma Goetz<sup>23</sup> noted roentgenologically a dilatation of the middle third and a narrowing of the lower third of the esophagus, esophageal ulceration, lack of peristalsis and stasis in the duodenum, dilatation of individual loops of the small intestine and extreme narrowing of the large bowel. Autopsy revealed involvement of all these areas.

*Carcinoma.*—Three cases of carcinoma of the esophagus are described, illustrating some of the problems associated with the disease.<sup>24</sup>

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22. Neuhauser, E. B. D., and Berenberg, W.: Cardio-Esophageal Relaxation as a Cause of Vomiting in Infants, *Radiology* **48**:480-483, 1947.

23. Goetz, R. H.: The Pathology of Progressive Systemic Sclerosis (Generalized Scleroderma), with Special Reference to Changes in Viscera, *Clin. Proc.* **4**:337-392, 1945.

24. Puppel, I. D.: Early Diagnosis in Radical Resection of Carcinoma of the Lower Esophagus, *Am. J. Surg.* **73**:695-699, 1947.

The number of successful resections continues to increase. Garlock<sup>25</sup> describes a new technic of combined abdominothoracic approach; Sweet<sup>26</sup> prefers the transthoracic method, with incision of the diaphragm. Lewis<sup>27</sup> performs a combined abdominal and thoracic operation in one or two stages. The abdominal portion consists of mobilization of the upper half of the stomach and a Witzel jejunostomy performed through a left paramedian incision. The thorax is opened on the right side, the esophagus freed and the stomach drawn through a widened hiatus. The stomach is anchored by suturing to the anterior cut edge of the mediastinal pleura, permitting end to side esophagogastrostomy without tension on the suture line. Of 7 patients subjected to this procedure, 5 recovered immediately.

Thirteen patients were operated on through a transthoracic approach for lesions of the lower part of the esophagus and of the cardiac end of the stomach; 12 had carcinoma and 1 an inflammatory lesion.<sup>28</sup> Resection of the lower end of the esophagus and of portions of the stomach was feasible in 7 patients. Of these, 1 died after nine months of metastasis after obtaining temporary relief. Another was known to have metastasis six months after operation and is presumed dead. Four patients are well from six months to more than a year after operation. One man had gained 31 pounds (14 Kg.) eleven months after operation. Another patient is reported to be convalescing.

Carter and McGrath<sup>29</sup> prefer the transthoracic approach to the trans-abdominal route because of a wider exposure, easier access and easier removal of regional lymph nodes. Indications for this procedure are carcinoma of the cardiac portion of stomach, carcinoma of the lower two thirds of the esophagus, benign stricture, diverticula in the lower third of the esophagus and chronic ulcer of the cardiac end of the stomach. Jejunostomy, performed under local anesthesia as a preliminary procedure, aids in the restoration of nutritional balance and also affords an opportunity for exploration of the entire upper area of the abdomen for evidence of metastasis. In forty-two major esophageal operations

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25. Garlock, J. H.: Combined Abdominothoracic Approach for Carcinoma of Cardia and Lower Esophagus, *Surg., Gynec. & Obst.* **83**:737-741, 1946.

26. Sweet, R. H.: Carcinoma of the Mid-Thoracic Esophagus: Its Treatment by Radical Resection and High Intrathoracic Esophagogastric Anastomosis, *Ann. Surg.* **124**:653-666, 1946.

27. Lewis, I.: The Surgical Treatment of Carcinoma of the Esophagus, with Special Reference to a New Operation for Growths of the Middle Third, *Brit. J. Surg.* **34**:18-31, 1946.

28. Nagel, G. W., and Menke, J. F.: Transthoracic Operations for Neoplasms of the Esophagus and Stomach, *Surg., Gynec. & Obst.* **83**:657-666, 1946.

29. Carter, B. N., and McGrath, E. J.: Esophagogastrostomy for Lesions of the Upper End of the Stomach and Lower End of Esophagus, *S. Clin. North America* **26**:1125-1139, 1946.

by Kay the mortality rate was 2.4 per cent.<sup>30</sup> Humphrey<sup>31</sup> discusses the surgical treatment of 70 patients with carcinoma of the esophagus. Radical resection of the tumor was carried out in 33 cases, with an operative mortality rate of approximately 50 per cent. Rienhoff<sup>32</sup> describes 3 patients with a lye stricture, carcinoma at the level of the aortic arch and achalasia of the esophagus respectively who were successfully treated by the intrathoracic transplantation of the jejunum as a substitute for the esophagus. Favorable results are reported in the treatment of 2 patients with squamous cell carcinoma of the esophagus with a depth dose of 4,000 r administered over a period of four weeks.<sup>33</sup>

*Leiomyomas.*—Thirty-two of forty-four benign esophageal tumors found in 7,459 postmortem examinations performed at the Mayo Clinic were leiomyomas.<sup>34</sup> The authors recommend surgical removal of all such tumors because of the potential danger of malignant transformation.

#### STOMACH

*Gastric Secretion.*—Forsgren<sup>35</sup> measured gastric secretion by Ewald test meals at 8:00 a.m., 1:00 p.m. and 6:00 p.m. of the same day in 557 patients with tuberculosis. The values for acidity remained approximately the same in 191 cases; considerable variation was noted throughout the day in the remaining 366 cases. In general, there was a tendency for acidity to decrease later in the day. The author believes that at least two test meals should be given, one on a fasting stomach in the morning and another later in the day, if an accurate appraisal of gastric secretory function is to be obtained. Observations on his own gastric secretory activity from 1925 to 1929 and from 1942 to 1944 by Hoelzel<sup>36</sup> disclosed a slight decrease in acidity and a decrease of approximately 50 per cent in the volume of gastric secretion during the nineteen year period. The average gastric acidity increased after restriction of protein and decreased when the intake of protein was augmented. Emotional stress was accompanied with a decided increase in acidity, as revealed by routine single daily determinations. The initial daily acidity, determined within a half hour after rising, was usually higher than the average of five to nine determinations made throughout the day.

30. Kay, E. B.: Surgical Lesions of the Esophagus Seen in an Army Thoracic Surgery Center, *J. Thoracic Surg.* **16**:207-214, 1947.

31. Humphrey, G. H.: An Approach to Resections of the Esophagus and Gastric Cardia, *Ann. Surg.* **124**:288-300, 1946.

32. Rienhoff, W. F., Jr.: Intrathoracic Esophagojejunostomy for Lesions of the Upper Third of the Esophagus, *South. M. J.* **39**:928-940, 1946.

33. Borak, J.: Radiation Therapy of Cancer of the Esophagus, *Am. J. Digest Dis.* **13**:249-252, 1946.

34. Calmenson, M., and Clagett, O. T.: Surgical Removal of Leiomyomas of the Esophagus, *Am. J. Surg.* **72**:745-747, 1946.

35. Forsgren, E.: To What Degree Does Gastric Acidity Show a Tendency to Rise or Fall During the Day? *Acta med. Scandinav.* **128**:281-288, 1947.

36. Hoelzel, F.: The Fasting Gastric Contents as an Index of Gastric Functioning, *Am. J. Digest Dis.* **13**:284-290, 1946.

Neches<sup>37</sup> suggests that the increased gastric motility after burns in dogs may be due to two separate mechanisms, i.e., cholinergic and histaminic. Relatively large doses of atropine did not affect the augmented gastric secretion of the dog's stomach after burns. Obrink<sup>38</sup> states that the histamine concentration in the blood must be maintained at a constant level if a stimulating effect is to result. Such a constant level is reached only by slow continuous intravenous administration. In a Heidenhain pouch dog the gastric juice appears within four to six minutes after intravenous injection, but it does not reach a steady rate before twenty to thirty minutes; subsequently, an almost constant level can be maintained for hours.

Ihre<sup>39</sup> studied the gastric secretory response to histamine in a series of 264 patients, including 204 with duodenal ulcer (153 men and 51 women) and 60 with gastric ulcer (41 men and 19 women), utilizing a single tube and continuous suction of the stomach. The data are compared with results in 18 normal men and in 15 normal women. The volume of secretion was higher in men than in women of the group with duodenal ulcer. The values for men with gastric ulcer were higher than those for women, but the differences were not as marked. In the normal group there was no difference between the two sexes. The mean volumes of secretion in the group with duodenal ulcer exceeded those for patients with gastric ulcer and for normal persons. The values in men with gastric ulcer exceeded those in normal men. Hypersecretion (defined as a secretion volume of more than 180 cc. per sixty minutes) was found in 77 cases and more often in men than in women. The maximum acidity in any of the three twenty minute samples was of less significance than the volume of secretion inasmuch as the mean for normal persons was higher than that for patients with duodenal ulcer. A comparison between the histamine tests and the gastroscopic findings demonstrated that acidity values below 90 to 100 milliequivalents at a secretion volume of at least 50 cc. per sixty minutes indicate the presence of chronic gastritis. Acidity values above 100 milliequivalents, on the other hand, do not exclude the diagnosis of gastritis. Values up to 130 or 140 milliequivalents are considered indicative of a normal gastric mucosa.

The concentration of hydrochloric acid and the total volume of histamine-stimulated secretion were not significantly reduced by administration of "benadryl hydrochloride."<sup>40</sup>

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37. Neches, H.; Prescott, E., and Olson, W. H.: The Effect of Atropine on the Gastric Secretion Following Thermal Trauma, *Surgery* **20**:382-384, 1946.

38. Obrink, K. G.: Some Relations in Gastric Stimulation by Intravenous Injection of Histamine, *Acta physiol. Scandinav.* **12**:213-218, 1946.

39. Ihre, B. J. E.: Studies in Gastric Secretion with an Improved Histamine Test, *Acta med. Scandinav.* **128**:322-340, 1947.

(Footnotes continued on next page.)

Musick and his associates,<sup>41</sup> confirming Ivy's work, found that caffeine stimulated secretion of hydrochloric acid in 10 apparently normal persons and produced an excessive prolonged secretory response in 25 patients with active duodenal and gastric ulcer.

The intravenous administration of moderate doses of quinine sulfate (0.2 to 0.3 Gm. to dogs weighing 10 to 15 Kg.) or of quinacrine hydrochloride (0.05 to 0.1 Gm. to dogs weighing 8 to 12 Kg.) markedly diminished the gastric secretion produced by rhythmic vagal stimulation;<sup>42</sup> small or moderate doses of quinine or of quinacrine hydrochloride did not affect histamine secretion.

In 56 patients the gastric free acidity was higher after graduated doses of protein hydrolysate than it was after an Ewald test meal, from which Rossien<sup>43</sup> concludes that the preparation is not an effective antacid.

The effects of vagotomy on secretion and motility of the stomach were studied in 10 dogs for periods of ten to fifty-seven months;<sup>44</sup> a reduction in secretion occurred in 9 of the 10. The response to histamine was permanently decreased during the period of observation. In most cases a gradual increase in the response to test meals was observed six months after vagus section; the secretion did not reach preoperative levels, however, and again decreased after a few years. Peptone added to test meals failed to stimulate acid secretion. This together with the observation that the histamine response was diminished led to the deduction that not only was the psychic phase of secretion lost but also the activity of the secretory mechanism of the stomach itself was reduced. The effect on motility was inconstant and variable; in general, motility tended to return to normal after variable periods. Vomiting or diarrhea or both, with loss of weight despite normal appetites, occurred in 4 dogs. Restoration of secretion was not due to regeneration of the vagi or to splanchnic innervation.

Wolf and Andrus<sup>45</sup> describe an important study of the effect of vagotomy on gastric function as observed through a fistula (gastrostomy)

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40. Moersch, R. U.; Rivers, A. B., and Morlock, C. G.: Some Results of the Gastric Secretory Response of Patients Having Duodenal Ulcer Noted During the Administration of Benadryl, *Gastroenterology* 7:91-99, 1946. McElin T., and Horton, B. T.: Clinical Observations on the Use of Benadryl: Its Effect on Histamine Induced Gastric Acidity in Man, *ibid.* 7:100-107, 1946.

41. Musick, V. H.; Hopps, H. C.; Avey, H. T., and Hellbaum, A. A.: The Effect of Caffeine on Gastric Secretion, *South. M. J.* 39:651-658, 1946.

42. Babkin, B. P., and Karp, D.: Effect of Quinine and Atabrine on Gastric Secretion *Canad. M. A. J.* 56:137-141, 1947.

43. Rossien, A. X.: An Evaluation of the Antacid Activity of Protein Hydrolysate Using Graduated Doses in the Human Stomach, *Am. J. Digest Dis.* 14:205-207, 1947.

44. Vanzant, F. R.: The Late Restoration of Gastric Acidity After Thoracic Vagotomy in the Dog, *Gastroenterology* 8:768-773, 1947.

45. Wolf, S., and Andrus, W. DeW.: The Effect of Vagotomy on Gastric Function, *Gastroenterology* 8:429-434, 1947.

necessitated by an esophageal neoplasm. Sensations of pain, pressure, heat and cold induced by the proper stimuli, were not affected by vagotomy. Vigorous motor activity was accompanied with hyperemia but not with an increased acidity. After vagotomy the mucous membrane was usually pale and spontaneous motor activity was not observed. However, mild hyperemia and engorgement appeared after a meal. Induced feelings of anger and resentment prior to vagotomy produced hyperemia, engorgement and hypermotility but no increased acidity. After vagotomy anger and resentment caused no observable changes in gastric function. Injection of "prostigmine" prior to vagotomy resulted in striking acceleration of motor activity and in hyperemia of the mucosa, without an increase in acid secretion. After vagotomy these effects were slight but still observable.

In a study of gastric secretion in the aged, Rafsky and Weingarten<sup>46</sup> found that of 47 apparently normal persons over 65 years of age, 53.2 per cent had 19 or less units of free hydrochloric acid after a bread and water test meal; achlorhydria was present in 17 per cent but not achylia gastrica, for milk-coagulating activity was present. Six patients, or 12.7 per cent, were found to have free acid values ranging from 50 to 90 clinical units. Rafsky and his co-workers<sup>47</sup> briefly review the conflicting evidence on the effect of thiamine deficiency on gastric acidity, present results of a study and conclude that it is questionable whether any causal relationship exists.

The chewing of gum temporarily reduced gastric acidity in 12 presumably healthy persons.<sup>48</sup>

Hypophysectomy is reported by Crafts and Walker<sup>49</sup> to have reduced the secretion in adult female rats from a control volume of 0.38 cc. to one of 0.23 cc.; the free acidity was lowered from 0.0037 to 0.0001 milliequivalents. Further studies of endocrine effects on gastric secretion would be interesting.

A simple, inexpensive and accurate method is presented for the measurement of pepsin and trypsin.<sup>50</sup> An improved method for the

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46. Rafsky, H. A., and Weingarten, M.: A Study of the Gastric Secretory Response in the Aged, *Gastroenterology* **8**:348-352, 1947.

47. Rafsky, H. A.; Lewman, B., and Jolliffe, N.: The Relationship of Gastric Acidity to Thiamine Excretion in the Aged, *J. Lab. & Clin. Med.* **32**:118-124, 1947.

48. Smith, C. S.; Wickoff, H. L., and Southard, M. E.: Some Effects of Gum Chewing on Gastric Acidity in Healthy Individuals, *Am. J. Digest Dis.* **13**:245-247, 1946.

49. Crafts, R. C., and Walker, B. S.: The Effects of Hypophysectomy on Gastric Acidity of Adult Female Rats, *Endocrinology* **40**:395-402, 1947.

50. Friedman, M. H. F.: A Simplified Procedure for the Determination of Pepsin and Trypsin Concentrations in Digestive Juices, *Gastroenterology* **8**:526-532, 1947.

measurement of total peptic activity of gastric juice is described by Le-Veen.<sup>51</sup> Egg albumin is used as substrate, and a photoelectric colorimeter, used as a densimeter, is employed to determine the amount of albumin solution digested. A method of greater sensitivity utilizes purified bovine and human serum albumin. The author<sup>52</sup> believes that the values for total pepsin of gastric juice give no indication of the digestive action in vivo as modified by inhibitory substances and „II. Total pepsin can be assayed only after high dilution of gastric juice, when it is completely freed from inhibitory peptones. Procedures are described whereby the amount of active pepsin, the percentage of pepsin inhibition and the active peptic power can be determined when they are used in combination with the test for total pepsin noted previously.

Brummer<sup>53</sup> states that the presence of achlorhydria is of indisputable value in the differential diagnosis between pernicious anemia and other macrocytic anemias. He believes that hydrochloric acid promotes the digestion of protein to some extent but apparently is not indispensable to it. Achlorhydria is not accompanied with disturbances in the motility of the stomach and the intestine or in the intestinal flora. Dyspeptic distress and a tendency to diarrhea are not more common in achlorhydric patients than in other persons. Therapeutic results supposedly obtained with hydrochloric acid do not prove that the latter is necessary for digestion, because the usual therapeutic doses have no effect on the reaction of the gastric contents. Thus achlorhydria is of no great importance from the standpoint of digestion or as a cause of digestive disturbances. The reviewers are in complete accord with these observations.

Brummer<sup>54</sup> presents a new method of determining the content of mucin in gastric juice. In this procedure the proteins are first precipitated with picric acid, the mucin then being precipitated from the filtrate with alcohol. The grade of turbidity thus obtained is used as a standard for the mucin content. In studies of 313 specimens obtained from 145 persons, 50 healthy and 95 suffering from various gastric disorders, the mucin content of the gastric juice varied from 0.15 to 1.5 per cent, with an average of approximately 0.5 per cent. The mucin content was slightly higher in the juice after a test meal than in the fasting juice. Histamine and insulin appeared to have no effect on the mucin content. No significant difference was found in the various gastric disorders. The mucin con-

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51. LeVeen, H. H.: Total Peptic Activity of Gastric Juice: A Method of Determination, *Proc. Soc. Exper. Biol. & Med.* 63:254-259, 1946.

52. LeVeen, H. H.: Active Pepsin Fraction, Resting Peptic Activity, and Percentage of Pepsin Inhibition in Gastric Juice, *Proc. Soc. Exper. Biol. & Med.* 63:259-263, 1946.

53. Brummer, P.: Clinical Significance of Achlorhydria, *Ann. med. int. Fenniae* 36:9, 1947.

54. Brummer, P.: On the Mucin Content of Gastric Juice, *Acta med. Scandinav.* 126:384-392, 1946.

tent of the gastric juice of patients with peptic ulcer and in those with gastritis was within the normal range.

No statistically significant stimulation of mucus secretion by the pyloric mucosa was observed after injections of pilocarpine.<sup>55</sup>

Repeated application of a 5 per cent eugenol-water emulsion to the pouch mucosa of a fasting dog results in progressive denudation of the protective layer of columnar cells and of many of the neck chief cells in parts of the mucosa.<sup>56</sup> By the time the fourth application is made the mucous barrier is seriously impaired; the disturbance persists for at least three months. After the sixth application there is evidence of a considerable inflammatory reaction of the tissue.

Hollander and others<sup>57</sup> found a 1 per cent emulsion of mustard oil in water to be an unsatisfactory stimulus for gastric mucus secretion; it acts as an active mucosal irritant, inducing an inflammatory reaction as well as a mucoid response. The gastric secretion produced is pinkish and congeals quickly and is predominantly a serous transudate.

*Gastric Motility and Absorption.*—Van Liere<sup>58</sup> and his associates report that the addition of glucose to a standard test meal for 19 young men prolonged gastric emptying to a degree roughly proportional to the amount ingested. Twenty-five grams produced 21 per cent prolongation above the norm, 50 Gm. a 39 per cent prolongation and 75 Gm. a 51 per cent prolongation.

The amount of glucose emptied from the stomach was greater and the absorption smaller when large volumes of dilute solutions of dextrose were given than when small volumes of concentrated solutions were administered, the total amount of dextrose fed being constant.<sup>59</sup> With identical concentrations, greater absorption and emptying was observed when larger volumes were used. With identical volumes, greater absorption and emptying was observed from the more concentrated solutions.

Studies on gastric motility in 8 normal young men indicated that, within nutritionally reasonable limits, increasing the proportion of the calories

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55. Ivy, J. S.: The Effect of Pilocarpine on Mucus Secretion by the Pyloric Mucosa, *Gastroenterology* 7:224-230, 1946.

56. Hollander, F.; Sonnenblick, B. P., and Sober, H. A.: Experimental Impairment of the Gastric Mucous Barrier in Dogs, *J. Nat. Cancer Inst.* 7:361-364, 1947.

57. Hollander, F.; Lauber, F. U., and Stein, J.: Some Characteristics of Gastric Secretion Induced by Mustard Oil Suspension, *Am. J. Physiol.* 149:724-731, 1947.

58. Van Liere, E. J.; Northup, D. W., and Stickney, J. C.: The Effect of Glucose on the Motility of the Stomach and Small Intestine, *Gastroenterology* 7:218-223, 1946.

59. Birchall, E. F.; Fenton, P. F., and Pierce, H. B.: Gastric Emptying and Intestinal Absorption of Dextrose Solutions, *Am. J. Physiol.* 146:610-612, 1946.



in the test meal from fat, protein or carbohydrate did not significantly alter gastric motility.<sup>60</sup>

According to Annegers and Ivy,<sup>61</sup> a person with a given volume of gastric contents has a reliably constant gastric shadow area when the stomach is outlined with a small amount of barium. This area varies with changes in the gastric content. A method based on these observations has been devised whereby variations in the rate of gastric evacuation in a given person may be determined by the measurement of the shadow areas with a planimeter after variation of the test meal or administration of drugs. Evaluation of the rate of gastric emptying by means of fluoroscopic examination, gastric intubation and determination of blood concentrations of test drugs indicated to Lolli and Smith<sup>62</sup> that effervescent mixtures decrease the emptying time of the stomach.

Harris and his associates<sup>63</sup> found that fat in the intestine inhibits gastric motility induced by distention in both vagally innervated and vagally denervated stomachs. Intravenously administered urogastrone and enterogastrone extracts inhibit the distention-induced motility of the vagally innervated stomach but either have no effect on the vagally denervated stomach or stimulate motility in it.

By means of electrodes placed in the mucosa and submucosa of the stomach, potential differences were studied under various conditions by Rehm.<sup>64</sup> Changes in potential noted after the injection of histamine and thiocyanate were due to changes in the potential difference between submucosa and mucosa; alcohol when applied directly to the submucosa created no significant changes in potential between mucosa and submucosa. It is concluded that the electromotive force originates in the secretory portion of the stomach.

*Gastric Cytology.*—A new technic for studying the cytologic elements in gastric contents is described, in which smears are stained with toluidine blue;<sup>65</sup> the columnar cells are better preserved by this procedure.

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60. Henschel, A.; Keys, A.; Sturgeon, A. M., and Taylor, H. L.: The Influence of Test Meal Composition on Gastric Emptying in Man, *Am. J. Physiol.* **149**:107-111, 1947.

61. Annegers, J. H., and Ivy, A. C.: A Method for Determining the Effect of Various Agents on Gastric Evacuation in Man, *Gastroenterology* **8**:711-716, 1947.

62. Lolli, G., and Smith, R.: Effervescent Mixtures as Adjuvants to the Rapid Absorption of Ingested Drugs, *New England Med.* **235**:80-84, 1946.

63. Harris, S. C.; Grossman, M. I., and Ivy, A. C.: The Role of the Vagus Nerves in the Inhibition of Gastric Motility by Fat and by Intestinal and Urinary Extracts, *Am. J. Physiol.* **148**:338-343, 1947.

64. Rehm, W. S.: Evidence That the Major Portion of the Gastric Potential Originates Between the Submucosa and Mucosa, *Am. J. Physiol.* **147**:69-77, 1946.

65. Hollander, F.; Hess, M., and Sober, H. A.: New Technique for Studying the Cytology of Gastric Aspirates in Man, *J. Nat. Cancer Inst.* **7**:365-366, 1947.

In a two hundred page article containing numerous tables and illustrations Tomenius<sup>66</sup> attempts to correlate gastroscopic findings with studies of the sediment of gastric juice. With the use of a four channel gastric tube, secretions were aspirated from the esophagus, stomach and duodenum through three of the channels, and through the fourth an isotonic (1.3 per cent) solution of sodium bicarbonate was introduced into the stomach by continuous flow. Aspirations were made by an apparatus maintaining a negative pressure subject to the operator's control. Examination of the sediment in 26 "normals" disclosed the presence of squamous cells in at least 47 per cent of the total number of samples; large pigmented cells (contamination from the respiratory passages) occurred in 7.3 per cent, red blood corpuscles in 3.8 per cent, columnar epithelium in 3 per cent and leukocytes in only 1.7 per cent. Study of 16 cases of gastritis (excluding atrophy) disclosed an increased number of cells, especially leukocytes. The cytologic picture in the 7 cases of atrophic gastritis and in the cases of peptic ulcer resembled that in normal cases. An increase in leukocytes and in red blood corpuscles was noted in the patients with cancer of the body of the stomach. In cases of cancer of the cardia there was an increase in squamous cells but not in leukocytes.

Varying results are reported on the accuracy of cytologic study of the gastric contents as an indication of gastric disease. In one investigation the gastroscopic findings were correlated with the cytologic changes in the gastric juice in 68 patients with gastritis and gastric ulcer.<sup>67</sup> A relationship was noted between the increase in the number of the leukocytes in the gastric juice and the degree of alteration in the mucosa. On the other hand, a study of the cells in the gastric secretion of normal persons and of patients with duodenal ulcer, gastric ulcer and gastritis revealed no correlation between the number of cells and the various diseases.<sup>68</sup>

*Effect of Drugs, Nausea and Emotions.*—Wolf and Wolff,<sup>69</sup> studying the action of drugs and various chemical agents on the gastric mucosa and the gastric function in man, found that while alkalis, acids, condiments and drugs such as digitalis, aminophylline, ammonium chloride, ferrous sulfate, and the sulfonamide compounds produced irritation when applied locally to the skin no irritation resulted from their application to the gastric mucosa. During the vasoconstriction produced by epinephrine and "benadryl hydrochloride," the mucosa was resistant to scratching from a dry gauze or to a blow from a blunt glass rod. Local application

66. Tomenius, J. H.: A Study on the Gastric Sediment, *Acta med. Scandinav.* 1947, supp. 189, pp. 1-402.

67. von Kapp, H.: Die diagnostische Bedeutung der Zelluntersuchung des Magensaftes, *Gastroenterologia* 71:289-294, 1946.

68. Altamira, J. del V., and Rennella, M.: Citologia del contenido gastrico en condiciones normales y patologicas, *Rev. med. de Cordoba* 35:8-22, 1947.

69. Wolf, S., and Wolff, H. G.: Action of Drugs and Various Chemical Agents on the Gastric Mucosa and Gastric Function in Man, *New York State J. Med.* 46:2509-2512, 1946.

of a 0.5 per cent solution of copper sulfate produced edema, engorgement and minute hemorrhages in the mucosa; under these conditions the mucosa was less resistant and easily damaged by mechanical injury. Peripherally acting emetics induced nausea only after reaching the duodenum.

The occurrence of nausea among soldiers overseas was found to accompany emotional reactions to adverse life situations.<sup>70</sup> Fear, despondency or a feeling of defeat were accompanied with a desire to reject the offending situation. Fluoroscopic observations on the barium-filled stomach and intragastric balloon studies tended to show that vomiting was brought on by the force of contraction of the diaphragmatic and abdominal musculature rather than by activity of the stomach. Nausea was accompanied with a decrease in the contractile state of the stomach and by cessation of motor activity.

The authors describe new experiments confirming earlier observations indicating the occurrence of two types of disturbances in the stomach in response to threatening situations.<sup>71</sup> These patterns are characterized by either overfunctioning or underfunctioning of the organ. Gastric hyperactivity was found to be frequently associated with heartburn and gnawing epigastric pain, characteristically more intense during periods when the stomach was empty and usually relieved by the taking of food, milk or alkali. Gastric hypoactivity was found to be accompanied with feelings of fulness in the epigastrium and nausea. The principal difference between the emotional reactions accompanying gastric hyperfunction on the one hand and hypofunction on the other appears to be in whether or not the subject accepts defeat in the adverse situation. The person whose stomach is hyperactive is physiologically prepared for food whether or not he has an appetite; he is angry, preparing for either fight or flight. The person whose stomach is hypoactive is not accepting the challenge of the situational threat. He considers himself defeated; the nausea expresses his rejection of the situation.

*Uropepsin.*—Uropepsin, a pepsin-like enzyme, in urine has been studied chiefly by German physiologists and clinicians. Bucher<sup>72</sup> undertook to verify its existence and stability and to confirm and evaluate some of the factors reported to produce variations in its excretion in normal persons. Assay was carried out by measuring the amount of tyrosine released from the digestive action of urine on a hemoglobin substrate. The

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70. Wolf, S.: Observations on the Occurrence of Nausea Among Combat Soldiers, *Gastroenterology* 8:15-18, 1947.

71. Wolf, S., and Wolff, H. G.: An Experimental Study of Changes in Gastric Function in Response to Varying Life Experiences, *Rev. Gastroenterol.* 14:419-426, 1947.

72. Bucher, G. R.: Uropepsin: A Review of the Literature and Report of Some Experimental Findings, *Gastroenterology* 8:627-647, 1947.

$p_H$  range for optimal digestion of hemoglobin substrate by uropepsin is tentatively 2.0 to 3.4. Uropepsin, regardless of the  $p_H$  of the urine, is stable for up to fifteen days if refrigerated after collection under toluol. Uropepsin, in contrast to pepsin, occurs in alkaline urine. Diet may significantly alter uropepsin output; a doubled protein intake markedly increases the output whereas restriction of protein reduces it. A milk diet containing amounts of protein similar to those in diets for the control group produced no appreciable change in uropepsin excretion. The output of uropepsin was distinctly higher during periods of emotional stress.

*Diaphragmatic Hernia.*—Among 53 patients with paraesophageal hiatus hernia women predominated in the proportion of 3 to 2; only 3 were under 50 years of age.<sup>73</sup> The chief symptom was distress after eating, especially after heavy meals. Occasionally there was pain in the epigastrium or behind the lower portion of the sternum. Pain was sometimes precipitated or aggravated by lying down, while relief followed rising or walking. In 2 cases there was moderate retrosternal pain referred to the left shoulder and arm, suggesting angina. Severe and prolonged hemorrhage occurred in 3 instances. Severe pain, frequent vomiting, anemia or interference with respiration or circulation are considered indications for surgical treatment. Satisfactory results were obtained in 14 of 16 cases in which surgical treatment was given. Codounis<sup>74</sup> reviews the subject in detail and emphasizes the desirability of surgical intervention in cases in which there is severe anemia.

*Volvulus.*—Three cases of detorsion of a chronic gastric volvulus during roentgen examination are described.<sup>75</sup>

*Diverticula.*—Ferguson and Cameron<sup>76</sup> present a technic for the treatment of diverticula consisting of invagination of the diverticulum, with suture of the muscular ring. This procedure was applied successfully in 5 cases, in 2 of which there was diverticula of the stomach and in 3 diverticula of the duodenum.

*Gastroscopy.*—A simultaneous roentgenologic and gastroscopic examination was performed on 3 patients. Gastroscopy was performed in a routine manner, and roentgenograms were taken in the left lateral and anterior projections which recorded the position of the gastroscope when important landmarks were seen through the instrument.<sup>77</sup> It was

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73. Trueman, K. R.: Diagnosis and Treatment of Para-Esophageal Hiatus Hernia, *Canad. M. A. J.* **56**:149-153, 1947.

74. Codounis, A.: Contribution a l'étude des syndromes anemiques des hernies diaphragmatiques, *Acta gastro-enterol, belg.* **10**:179, 1947.

75. Chaumerliac, H., and Duperrier-Nigon: Detorsion de trois cas de volvulus chronique de l'estomac observée au cours de l'examen radiologique, *Acta gastro-enterol. belg.* **9**:249-253, 1946.

76. Ferguson, L. K., and Cameron, C. S.: Diverticula of the Stomach and Duodenum, *Surg. Gynec. & Obst.* **84**:292-300, 1947.

77. Ould, C. L., and Dailey, M. E.: Simultaneous Radiographic and Gastroscopic Examination of the Stomach, *Radiology* **48**:8-14, 1947.

calculated that 1,500 to 2,000 cc. of air may be introduced into the stomach in a routine gastrosocopy. The roentgenograms demonstrated a considerable amount of air distending not only the stomach but also the duodenum and the upper part of the small intestine. The air in the small bowel, increasing as the examination progresses, pushes the stomach anteriorly and may distort its lower pole. These alterations may explain the failure of inexperienced gastroscopists to visualize the pylorus. Passage of the instrument beyond the cardia was along the posterior wall in 1 instance, always contacting the mucosa; in another it was carried through the lumen and did not impinge on the posterior wall until the lower third of the stomach was reached; in the latter instance, the posterior blind area was smaller than in the first instance.

Fluorescein proved to be a helpful adjunct in the gastroscopic visualization of a gastric ulcer in 4 cases.<sup>78</sup> The procedure consists in the administration of 10 cc. of the dye through the Ewald tube after emptying of the stomach; the ulcers assume a greenish fluorescence and thus are more easily detected.

Moersch<sup>79</sup> comprehensively reviews the value of gastroscopy in the diagnosis of various gastric diseases. Similar discussions are presented by Monat and Thompson<sup>80</sup> and by Jones.<sup>81</sup> The group for whom gastroscopic examination is indicated in the army, as defined by Chamberlin,<sup>82</sup> consists of patients with typical intragastric disease who could be used for teaching purposes, those with obscure or doubtful lesions (for the purpose of more accurate diagnosis) and those without roentgenologically demonstrable disease (in order to make a diagnosis).

Benedict<sup>83</sup> analyzes the limitations of gastroscopy and roentgenology in the differential diagnosis of benign and malignant lesions of the stomach on the basis of a series of 53 patients with proved gastric disease, including 19 with carcinoma, 21 with benign gastric ulcer, 2 with jejunal ulcer, 5 with gastritis, 2 with benign tumors, 1 with lymphoma, 1 with a posterior gastroenterostomy stoma and 2 with a normal stomach. In 19

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78. Robinson, H. M.: Fluorescein: An Aid in Gastroscopy, *Rev. Gastroenterology* **13**:303-305, 1946.

79. Moersch, H. J.: The Value of Gastroscopy in the Diagnosis of Gastric Disease, *M. Clin. North America* **30**:903-911, 1946.

80. Monat, H. A., and Thompson, C. M.: Evaluation of Gastroscopic, Roentgen, Sigmoidoscopic and Laboratory Procedures in Five Hundred Gastrointestinal Cases, *Rev. Gastroenterol.* **13**:19-21, 1946.

81. Jones, C. M.: The Value of Gastroscopy to the Clinician, *Gastroenterology* **8**:278-283, 1947.

82. Chamberlin, D. T.: Criteria for Gastroscopic Examination in the Army, *Gastroenterology* **8**:131-134, 1947.

83. Benedict, E. B.: The Limitations of Roentgenology and Gastroscopy in the Diagnosis of Diseases of the Stomach: An Analysis of Fifty-Three Proven Cases, *Gastroenterology* **8**:251-277, 1947.

cases of proved carcinoma the roentgenologic and gastroscopic diagnoses were both correct in 10 instances. In 1 case a malignant ulcer was interpreted as benign by both methods. In 1 case the disease was doubtfully malignant as judged by the roentgenologic evidence and appeared benign at gastroscopy. Gastroscopy failed to visualize an ulcerating neoplasm in another patient. Gastroscopy revealed the true nature of the lesion in 6 cases in which the roentgenologic diagnosis was doubtful. Of 21 instances of benign gastric ulcer, the disease was correctly diagnosed in 8 by both the radiologist and the gastroscopist; both procedures resulted in incorrect diagnosis in 5 cases. Gastroscopy failed to visualize the lesion in 5 cases, and in 1 an erroneous diagnosis of malignancy was made. In 2 cases the gastroscopist diagnosed benign lesions previously interpreted as malignant on roentgenologic examination. It was difficult to correlate the roentgenologic, gastroscopic and pathologic findings in the 5 cases of gastritis. In summary, both methods resulted in correct diagnosis in 21 cases and in incorrect diagnosis in 8. Gastroscopy was more correct in 13 cases and roentgen examination more correct in 11. In 8 of the latter visualization was inadequate because of mechanical limitations. It is concluded and emphasized that the two methods are mutually helpful and that greater diagnostic accuracy is obtained when both are utilized.

*Experimental Gastritis.*—Antral and fundic lesions were produced in rats by the use of diets deficient in calcium and vitamin B. Alterations in the mucosal vessels were demonstrated by injections of india ink. The antral lesions corresponded to changes found in human antral gastritis, and the fundic lesions were similar to hemorrhagic erosions in man.<sup>84</sup>

*Symptoms in Patients with Gastritis.*—One hundred and ten consecutive and unselected patients complaining of "chronic dyspepsia" were studied by clinical, roentgenologic, psychiatric and gastroscopic examination.<sup>85</sup> Fifty-nine per cent had a normal gastric mucosa. In 41 per cent there were mild to moderate abnormalities, consisting of redness, exudation and edema. There was no correlation between the appearance of the mucosa and the symptomatology, the symptoms being the same whether or not the mucosa was normal. Approximately 85 per cent of the total and 75 per cent of those with gastroscopic abnormalities had psychoneurosis. The authors interpret the gastroscopic changes as evidence of functional circulatory alterations resulting from nervous tension rather than as evidence of organic disease.

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84. Berg, B. N.: Vascular Changes in the Mucosa in Experimental Nutritional Gastritis, *Gastroenterology* 7:340-354, 1946.

85. Halsted, J. A.; Schwartz, I. R.; Rosen, S. R.; Weinberg, H., and Wyman, S. M.: Correlated Gastroscopic and Psychiatric Studies of Soldiers with Chronic Non-Ulcerative Dyspepsia, *Gastroenterology* 7:177-190, 1946.

One hundred and fifty records of patients with the gastroscopic diagnosis of gastritis, including the records of 50 cases each of atrophic, hypertrophic and superficial gastritis, were reviewed by Horner.<sup>86</sup> Approximately 80 per cent of each group described some form of epigastric distress. Pain was present in 80 per cent of the patients with hypertrophic gastritis, in 66 per cent of those with superficial gastritis and in none of the group with atrophic gastritis. In 71 per cent of the last group the chief symptom was "fulness" or "pressure." The taking of food or alkali provided relief from pain in half of the group with hypertrophic gastritis and in one fourth of the group with superficial gastritis. Nausea and vomiting were present in about one third of each group. Weight loss was most frequent (30 per cent) in the series with atrophic gastritis and was noted in only 12 per cent of each of the other two groups. The findings are interpreted as suggestive but not conclusive evidence that gastritis is directly concerned in the production of epigastric distress.

Fifty-eight patients with previously diagnosed functional gastrointestinal disease were subjected to gastroscopic study.<sup>87</sup> A diagnosis of gastritis was made in 25; it was hypertrophic in 11, atrophic in 7 and superficial in 7. In the remaining 33 the gastroscopic findings were normal. The clinical features in 25 of this group were compared with those in the "gastritis" group. Nausea, belching, bloating, anorexia and vomiting were the most common symptoms in both groups. Loss of weight exceeding 10 pounds (4.5 Kg.) had occurred in 7 of the group with gastritis. Epigastric tenderness was present in members of both groups. Gastric acidity varied widely and was unrelated to the presence or absence of gastritis. There was, however, a distinct tendency for the group with atrophic gastritis to secrete less acid than the others. Both groups were placed on essentially the same therapeutic regimen, namely a bland, low residue diet, with liver and vitamins, and avoidance of hot and cold foods, tobacco and alcohol. Each of the patients with gastritis admitted that they experienced at least a 50 per cent improvement, although 3 with chronic hypertrophic gastritis and 1 with atrophy showed no improvement on gastroscopy. Two with atrophic gastritis and 6 with superficial gastritis were rendered asymptomatic, and in 4 of the latter the gastritis apparently subsided. Of the group with functional gastric disease, none felt 50 per cent better, 7 were 25 per cent improved, 16 described no change and 10 were worse.

The varying interpretations drawn from these three studies are consistent with the experience of the reviewers. The evaluation of symptoms in patients with gastritis is often extremely difficult. Although chronic gastritis seems to be more prevalent in patients with discomfort

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86. Horner, J. L.: The Symptomatology of Chronic Gastritis, *Gastroenterology* 8:607-611, 1947.

87. Palmer, E. D.: The Chronic Gastritis Problem: Functional Upper Gastrointestinal Disease in Military Personnel and the Value of Establishing an Organic Basis for Diagnosis and Treatment, *Gastroenterology* 8:743-753, 1947.

in the upper abdominal area, it is not infrequently encountered in patients with distress in the lower abdominal area or with complete absence of symptoms. Furthermore, the gastric mucosa may appear normal gastroscopically in persons with severe distress.

*Large Gastric Rugae.*—Ricketts, Kirsner and Palmer<sup>88</sup> direct attention to the fact that large but otherwise normal gastric rugae may roentgenologically simulate the appearance of neoplasm of the stomach. Gastroscopic examination in 3 cases demonstrated the benign nature of the rugae. The large pliable folds returned to normal size in 2 cases after insufflation of air and in the third case after subsidence of peristaltic activity. There was no evidence of gastritis as noted gastroscopically. A somewhat similar case, without gastroscopic observation, is reported by Maissa and Centeno.<sup>89</sup>

*Hypertrophic Gastritis.*—Two instances of hypertrophic gastritis roentgenologically simulating neoplasm of the stomach are reported;<sup>90</sup> the diagnoses were based on histologic examination.

Six well studied cases of giant hypertrophic gastritis, in 2 of which there was superimposed hyperplastic polyp formation, are described by Maimon and his associates.<sup>91</sup> The symptomatology varied from vague abdominal or epigastric distress to a syndrome simulating ulcer with or without vomiting. Differential diagnosis was difficult, attested by the fact that all the patients were operated on because of the possibility of neoplasm. Gastroscopically, anatomically and roentgenologically the gastric folds resembled the convolutions of the brain. The histologic changes consisted of redundancy of the mucosa and hypertrophy of glandular structures, cyst formation and metaplasia to the intestinal type of epithelium. The cells forming pepsinogen and acid were replaced by more primitive cells. Multiple polyps developed in 2 cases.

Pyloric obstruction occurred as a complication of chronic hypertrophic gastritis in a 53 year old man.<sup>92</sup>

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88. Ricketts, W. E.; Kirsner, J. B., and Palmer, W. L.: Large, Otherwise Normal Gastric Rugae Simulating Tumor of the Stomach, *Gastroenterology* 8:123-130, 1947.

89. Maissa, P. A., and Centeno, A. M.: Imágenes pseudoneoplásicas por gastritis hipertrofica, *Arch. argent. de Enferm. d ap. digest y de la nutrición* 21:199-208, 1946.

90. Bank, J.; Pearce, A. E., and Gilmore, J. H.: Hypertrophic Gastritis Simulating Neoplasm, *Am. J. Digest Dis.* 13:344-346, 1946. Camena d'Almeida, P.: La biopsie de muqueuse gastrique sous contrôle gastroscopique, *Acta gastro-enterol. belg.* 9:497-502, 1946.

91. Maimon, S. N.; Bartlett, J. P.; Humphreys, E. M., and Palmer, W. L.: Giant Hypertrophic Gastritis, *Gastroenterology* 8:397-428, 1947.

92. Judd, E. S., and Moe, A. E.: Chronic Hypertrophic Gastritis Complicated by Obstruction: Report of Case, *Proc. Staff Mee., Mayo Clin.* 22:241-249, 1947.



*Atrophic Gastritis.*—Moutier and Martin<sup>93</sup> report two interesting observations of chronic atrophic gastritis associated with multiple erosions. The lesions were characterized roentgenologically by small round niches similar to those produced by benign polyps but umbilicated at their apexes. The umbilicated appearance was clearly visualized gastroscopically.

*Antral Gastritis.*—The difficulty of differentiating between antral spasm and antral gastritis as well as between these two conditions and carcinoma is emphasized by Rennie.<sup>94</sup>

*Congenital Pyloric Stenosis.*—Donovan<sup>95</sup> summarizes his experience with 507 cases of congenital hypertrophic pyloric stenosis. The mortality rate from surgical intervention was 1.8 per cent for the entire series and 0.8 per cent for the last 245 cases (1937 to 1946). Additional observations on this entity are presented by Chene and Spriet,<sup>96</sup> Akin and Forbes<sup>97</sup> and Todd.<sup>98</sup>

Hypertrophic pyloric stenosis occurred in a man of 46 with a four year history of epigastric distress.<sup>99</sup> Operation revealed considerable hypertrophy of the entire pyloric sphincter, producing almost total obstruction; a partial gastric resection was performed. The pyloric musculature on cross section measured 1.5 cm. in thickness. No emotional factors of etiologic significance were encountered.

Pyloric stenosis in binovular twins<sup>100</sup> is reported as an exception to the rule that when one is affected the other will not be.

Two cases of congenital pyloric stenosis were observed in a family of 3 children; both patients were boys and were the first two offsprings in the family, suggesting a hereditary factor.<sup>101</sup>

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93. Moutier, F., and Martin, J.: Deux cas de gastrite varioliforme, Arch. d. mal. de l'app. digestif **36**:154-160, 1947.

94. Rennie, J. W. R.: Antral Gastritis and Spasm: Their Clinical and Surgical Significance, Ann. Surg. **124**:402-409, 1946.

95. Donovan, E. J.: Congenital Hypertrophic Pyloric Stenosis, Ann. Surg. **124**:708-715, 1946.

96. Chene, P., and Spriet, R.: Les stenoses hypertrophiques benignes du pylore chez l'adulte, Arch. d. mal. de l'app. digestif **35**:285-302, 1946.

97. Akin, J. T., Jr., and Forbes, G. B.: Congenital Hypertrophic Pyloric Stenosis, Surgery **21**:512-522, 1947.

98. Todd, R. M.: Review of One Hundred and Twelve Cases of Congenital Hypertrophic Pyloric Stenosis, Arch. Dis. Childhood **22**:75, 1947.

99. Vorhaus, M. G.: Hypertrophic Pyloric Stenosis in the Adult, Gastroenterology **7**:464-468, 1946.

100. Laubscher, J. H., and Smith, A. M.: Pyloric Stenosis in Twins: Review of the Literature and Report of a Case, Am. J. Dis. Child. **73**:334-341 (March) 1947.

101. Kaufman, B.: Congenital Pyloric Stenosis. Report of Two Cases in a Family of Three Children, Arch. Pediat. **64**:1-5, 1947.

In 9 infants with congenital hypertrophic pyloric stenosis, alkalosis was successfully ameliorated by the intravenous or subcutaneous injection of a solution of ammonium chloride in one-sixth molar concentration in isotonic solution of sodium chloride.<sup>102</sup> Toxic effects consisting of pallor, muscular twitchings and bradycardia were observed in only 1 patient, in whom the material was injected intravenously at an excessively rapid rate.

*Pylorospasm.*—Brackett<sup>103</sup> regards pylorospasm and intestinal colic as abnormalities of the motor mechanism of the digestive tract. He found that both could be controlled by reducing the volume of food and evoked by increasing the quantity of food.

*Foreign Bodies.*—Sharp-pointed foreign bodies swallowed into the stomach should be treated conservatively, according to Best,<sup>104</sup> with careful observation and repeated fluoroscopic or roentgenologic examination. Only occasionally will surgical intervention be needed. Indications for surgical treatment include the appearance of signs and symptoms of impending perforation or a twenty-four to forty-eight hour delay of the foreign body at any fixed point. Removal of metallic foreign bodies from the stomach by means of an alvico permanent magnet is discussed, and its successful application in 1 case is described.<sup>105</sup>

Silber and Epstein<sup>106</sup> utilize a fluoroscopically guided alvico magnet attached to a Levine tube inserted into a large caliber rubber tube. This assembly is passed into the stomach, with the magnet protruding slightly. When the foreign body is firmly attached to the magnet, both are withdrawn as far as necessary into the end of the rubber sheath by pulling on the inner tube. Thus protected, the foreign body moves easily through all narrow places and safely past the open air passages.

*Gastroileostomy.*—Twenty-two cases of gastroileostomy previously described in the literature are reviewed, and 3 new ones are presented.<sup>107</sup> The predominant symptoms were weight loss, diarrhea, pain and vomiting, sometimes fecal in type. Hemorrhage occurred in 3; ileal ulcer was present in 6 of the 22 cases previously reported. Roentgenologic exami-

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102. Forbes, G. B., and Erganian, J. A.: Parenteral Administration of Ammonium Chloride for Alkalosis of Congenital Hypertrophic Pyloric Stenosis., *Am. J. Dis. Child.* **7**:649-660 (Dec.) 1946.

103. Brackett, A. S.: The Alleviation of Pylorospasm and Colic in Infants by Reducing the Volume of the Food Intake Per Feeding, *Yale J. Biol. & Med.* **19**:155-169, 1946.

104. Best, R. R.: Management of Sharp Pointed Foreign Bodies in the Gastro-Intestinal Tract, *Am. J. Surg.* **72**:545-549, 1946.

105. Kenamore, B.: Removal of Foreign Bodies from the Stomach with a Permanent Magnet, *Gastroenterology* **8**:90-91, 1947.

106. Silber, S., and Epstein, B. S.: The Peroral Removal of Certain Swallowed Foreign Bodies Without Endoscopy, *New York State J. Med.* **47**:1122-1124, 1947.

107. Brown, C. H.; Colvert, J. R., and Brush, B. E.: Gastro-Ileostomy: A Rare Surgical Error; Symptoms and X-Ray Findings, *Gastroenterology* **8**:71-81, 1947.

nation was helpful in diagnosis. In 2 of the 3 cases refilling of the stomach was observed after it had emptied. In 1 case the short loop of the ileum that passed directly from the stomach to the colon could be seen filled with barium. In 2 of the cases the condition responded promptly to simple disconnecting of the "gastroenterostomy." The third patient at operation was found to have a gastroileostomy opening within several inches of the ileocecal valve. Two marginal ulcers were present.

*Gastrocolic Fistula.*—Roentgen studies were carried out on 7 dogs with experimentally induced gastrocolic or enterocolic fistulas and on 10 patients with gastrocolic fistula.<sup>108</sup> All or the major portion of the aliment passed from the stomach into the upper intestine, and practically none was shunted through the fistula into the colon. Two to six months after the experimental operative procedure a syndrome developed in the dogs consisting of a microcytic hypochromic anemia, intermittent diarrhea, steatorrhea, loss of weight and malnutrition. Gastric inflammation was present in 5 and ulceration in 2 animals. A subacute to chronic inflammatory infiltration, limited almost exclusively to the mucosa of the papillae, was present in the upper third of the small intestine. There was a tendency for the microcytic anemia to become macrocytic and hyperchromic in those animals surviving for a sufficiently long time. In a later report<sup>109</sup> the clinical manifestations are attributed to impairment of the digestive and absorptive functions of the small intestines as a result of the passage of colonic contents through it.

*Ectopic Smooth Muscle.*—Lattes<sup>110</sup> found conspicuous bundles of smooth muscle in the mucosa of the antral region in 56 of 100 unselected stomachs surgically removed for various reasons.

*Tuberculosis.*—Tuberculosis of the stomach was diagnosed for a 35 year old woman with a persistent prepyloric roentgen defect, gastric retention and anacidity.<sup>111</sup> The diagnosis was confirmed by histologic examination of a lymph node removed from the lesser curvature of the stomach at operation. Two years later tuberculous ulcerative colitis developed and a granuloma of the rectum, which was removed and contained acid-fast bacilli. Roentgenograms of the lungs showed no evidence of pulmonary involvement.

*Gastric Arteriosclerosis.*—Episodes of severe intermittent gastric bleeding over a period of thirty years in a 44 year old man were found at autopsy to be caused by advanced arteriosclerosis of extraordinarily

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108. Renshaw, R. J. F.; Templeton, F. E., and Kiskadden, R. M.: *Gastrocolic Fistula: A Clinical and Experimental Study*, *Gastroenterology* 7:511-521, 1946.

109. Kiskaddon, R. M.; Templeton, F. E., and Renshaw, R. J.: *Gastro-Colic Fistula: A New Concept of Pathologic Physiology; Mechanism of Production of the Syndrome*, *Cleveland Clin. Quart.* 14:94-107, 1947.

110. Lattes, R. *Ectopic Smooth Muscle in the Human Gastric Mucosa*, *Am. J. Path.* 23:501-505, 1947.

111. Windwer, C.: *Tuberculosis of the Stomach*, *Rev. Gastroenterol.* 13:38-41, 1946.

large submucosal branches of the gastric arteries. Recurrent pulmonary tuberculosis was the cause of death.<sup>112</sup>

*Hereditary Hemorrhagic Telangiectasia.*—Kushlan<sup>113</sup> discusses the rare entity of hereditary hemorrhagic telangiectasia and presents observations made in 1 case, including gastroscopic findings. A favorable response to therapy with rutin apparently was obtained.

*Polyps and Miscellaneous Tumors.*—Ten gastric polyps and three additional possible polyps were found in 1,725 gastroscopic examinations.<sup>114</sup> The clinical features were not diagnostic. It is recommended that small asymptomatic polyps, appearing benign at gastroscopy, not be removed. Surgical intervention is indicated when there is a suggestion of malignancy, when the polyps are large or when complications such as obstruction occur. Similar views are expressed by Rappeport.<sup>115</sup> Interesting reports are presented of single polyps containing aberrant pancreatic tissue,<sup>116</sup> fibroma,<sup>117</sup> adenoma of the stomach,<sup>118</sup> gastric lipoma,<sup>119</sup> ganglioneuroma,<sup>120</sup> plasmacytoma producing complete pyloric obstruction<sup>121</sup> and an argentaffinoma causing gastroduodenal invagination.<sup>122</sup>

#### GASTRIC CANCER

*Survey of the Problem.*—In a comprehensive review of the problem

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112. Frank, W.: Hematemesis Associated with Gastric Arteriosclerosis, *Gastroenterology* 7:231-240, 1946.

113. Kushlan, S. D.: Gastro-Intestinal Bleeding in Hereditary Hemorrhagic Telangiectasia, *Gastroenterology* 7:199-212, 1946.

114. Paul, W. D., and Logan, W. P.: Polyps of the Stomach with Reference to the Gastroscopic Findings, *Gastroenterology* 8:592-606, 1947.

115. Rappeport, J. H.: Gastric Polyposis, *New Orleans M. & S. J.* 99:71-78, 1946.

116. Collett, R. W.: Prepyloric Polyp in Stomach of Child Diagnosed Histologically as Aberrant Pancreatic Tissue, *Am. J. Dis. Child.* 72:545-551 (Nov.) 1946. Barbosa, J. de C., and Waugh, J. M.: Heterotopic Pancreatic Tissue, Clinically Significant, in the Gastric Wall of a Boy Six Years of Age, *Proc. Staff Meet., Mayo Clin.* 22:25-30, 1947.

117. Rusker, W. H.: Fibroma of the Stomach, *Minnesota Med.* 29:1042-1044, 1946.

118. Brocher, J. E. W., and Queloz, M.: Sur un adenome de la petite courbure, *Gastroenterologia* 71:321-326, 1946. Colillas, D.; Bazterrica, E., and Garay, C. A.: Adenoma del estomago, *Bol. y trab. Acad. argent. de cir.* 30:387-398, 1946. Bonamy, M., and Rubens-Duval, A.: Adenomatose diffuse de la muqueuse gastrique, *Arch. d. mal. de l'app. digestif* 35:303-307, 1946.

119. Morichau-Beauchant, J.; Debelut, J., and Payard, J. M.: Image radiologique d'une tumeur intragastrique, *Arch. d. mal. de l'app. digestif* 35: 52-54, 1946.

120. Pitts, H. H., and Hill, J. E.: Case Reports: Ganglioneuroma of Stomach, *Canad. M. A. J.* 56:537-539, 1947.

121. Schwander, H.; Estes, J., and Cooper, W. G.: Plasmacytoma of the Stomach, *Am. J. Path.* 23:237-242, 1947.

122. Jungmann, H.: Gastro-Duodenal Invagination, *Brit. J. Radiol.* 19:292-296, 1946.

of gastric cancer, Barrett<sup>123</sup> points out that present statistics dealing with various experimental and clinical aspects are not entirely adequate. Further studies should be directed toward the role of genetic factors and the relationship of gastric cancer to pernicious anemia, achlorhydria and atrophic gastritis, diet and sex hormones. Proof of the exact relationship of gastric cancer to gastric ulcer is lacking, and additional experimental evidence on this problem is needed. New or improved methods for the diagnosis of early gastric cancer are urgently required. Investigation of the relation of mucus and bile to gastric cancer is desirable. The establishment of a gastric cancer registry might lead to more fruitful attacks on the problem. Ivy<sup>124</sup> subscribes to these views and in addition indicates the need for further education of the medical profession, surveys to find areas of high incidence and a more effective detection program.

*Experimental Observations.*—The repeated direct alimentary administration of hot water, hydrochloric acid, sodium hydroxide, lactic acid or atropine sulfate, with or without an emulsion of 1, 2, 5, 6-dibenzanthracene, failed to produce cancer or precancerous lesions in the gastric mucosa of mice of strains A, I and CsH and in hybrid LA mice (strain L crossed with mice of strain A).<sup>125</sup> Repeated parenteral injections of methyl chloride or of atropine sulfate, with and without direct alimentary administration of 1, 2, 5, 6-dibenzanthracene, were likewise ineffective in producing any specific pathologic changes in the gastric mucosa of mice. That the stomach showed so little injury after drastic treatment is evidence of the remarkable resistance and recuperative power of the mucosa.

Strong<sup>126</sup> presents additional data regarding the development of cancerous lesions in the gastric mucosa of 540 mice following the subcutaneous injection of methylnanthrene. The lesions have occurred in mice from the F5 to F18 generations inclusive. The author concludes that a hereditary disease or a hereditary susceptibility to a disease, gastric cancer in mice, has been induced with chemical means. A multiplicity of pathologic lesions arising just anterior to the pylorus are probably biologically related, all being derived from the same or from similar embryologic defects and very likely the resultant of a biologic variability brought about by (1) the process of hybridization and (2) the induction of germinal mutations by methylnanthrene or one of its metabolites.

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123. Barrett, M. K.: Avenues of Approach to the Gastric Cancer Problem, J. Nat. Cancer Inst. 7:127-157, 1946.

124. Ivy, A. C., in Discussion of a Comprehensive Outline of Attack on Gastric Cancer, J. Nat. Cancer Inst. 7:404-407, 1947.

125. Dyer, H. M.; Kelly, M. E., and Dunn, T. B.: Effect of Administration of Hot Water, Acids, Alkali, Methyl Chloride or Atropine Sulfate upon the Gastric Mucosa of Mice, J. Nat. Cancer Inst. 7:67-71, 1946.

126. Strong, L. C.: Further Observations on the Genetic Nature of Gastric Cancer in Mice, J. Nat. Cancer Inst. 7:305-308, 1947.

McPeak and Warren<sup>127</sup> describe in detail the gross and microscopic characteristics of the lesions and conclude that a definitive classification is not possible at the present time. The reviewers have failed to find evidence that the lesions described by Strong are in fact adenocarcinomas. Strong is a geneticist rather than a pathologist; the pathologists seem unconvinced. Consequently, final judgment with regard to this apparently important work must be deferred until conclusive pathologic proof is presented.

In experiments by Lushbaugh<sup>128</sup> 7 monkeys were exposed to a shale oil; 6 died during or shortly after the one hundred day exposure period. Hyperplastic gastritis, polyps and penetration of the submucosa by epithelial growths were found in the 2 monkeys surviving the longest; the seventh monkey, alive one and a half years later, was killed and found to have severe atrophic gastritis. The relationship of these types of gastritis to neoplasia remains to be determined; however, the preliminary observations suggest an interesting approach to this important problem.

The daily oral administration of 15 mg. of 20-methylcholanthrene to rabbits in which a "chronic" gastric ulcer had been produced surgically did not result in any detectable change in the ulcer in the domestic rabbits after periods of 3.5 to 5.5 months.<sup>129</sup> In similarly treated wild rabbits formation of epithelial cysts occurred in 3 of the 4 animals subjected to autopsy after five to thirteen months.

In a series of thirty-five experiments quinine was given either by mouth or by vein from two to six hours preoperatively to a group of patients with carcinoma of the tongue, esophagus, stomach or colon, and the tissues were studied for their quinine content.<sup>130</sup> The results suggest that quinine is selectively concentrated by neoplastic tissue, although the extent of the concentration is too small to be of any immediate significance.

The human stomach concentrates radioactive iodine to a considerable degree after the intravenous administration of 4 microcuries of radioiodine and 0.01 mm. of sodium iodide per kilogram of body weight.<sup>131</sup> The salivary glands excrete the radioiodine usually in higher concentration than the stomach. No definite conclusions can be drawn as yet con-

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127. McPeak, E., and Warren, S.: The Pathology of Gastric Carcinoma in Mice, *J. Nat. Cancer Inst.* 7:309-311, 1947.

128. Lushbaugh, C. C.: Experimental Hyperplastic Gastritis and Gastric Polypsis in Monkeys, *J. Nat. Cancer Inst.* 7:313-320, 1947.

129. Ivy, A. C., and Cooke, A.: An Attempt to Produce Malignant Transformation of Gastric Ulcer in Rabbits: A Preliminary Report, *J. Nat. Cancer Inst.* 7:345-348, 1947.

130. Kelsey, F. E., and Brunschwig, A.: Concentration of Quinine in Gastrointestinal Cancers: Preliminary Report, *J. Nat. Cancer Inst.* 7:355-356, 1947.

131. Schiff, L.; Stevens, C. D.; Mahl, W. E.; Steinberg, H.; Kumpe, C. W., and Stewart, P.: Gastric (and Salivary) Excretion of Radioiodine in Man: Preliminary Report, *J. Nat. Cancer Inst.* 7:349-354, 1947.

cerning the influence of gastric disease, such as cancer, other tumors and peptic ulcer on the ability of the stomach to concentrate radioiodine.

*Pernicious Anemia and Gastric Cancer.*—In serial roentgenologic and gastroscopic examination of 211 patients with pernicious anemia, described by Rigler and his associates two years ago, 17 (8.0 per cent) were found to have carcinoma and 15 (7.1 per cent) benign polyps. Since then 48 new patients with pernicious anemia have been examined, with demonstration of one additional cancer and two benign polyps. These data provide further evidence that carcinoma of the stomach is more prevalent among persons with pernicious anemia than among the general population. The nature of this relationship remains obscure, but the evidence suggests that the two diseases are related etiologically.<sup>132</sup>

Benedict<sup>133</sup> points out that gastric atrophy is a definite disease possibly caused in part by an inflammatory process and in part by a state of deficiency. Gastroscopically, there is evidence that in some cases the gastric mucosa improves after prolonged, intensive liver therapy; pathologic proof of such improvement thus far has not been obtained. The high incidence of neoplasm in patients with gastric atrophy is again borne out.

*Gastric Secretion.*—In an attempt by State, Varco and Wangenstein<sup>134</sup> to identify the precursors of gastric cancer, gastric analyses were performed for 1,253 patients over the age of 50; achlorhydria to three successive 0.5 mg. doses of histamine was found in 238 and to one dose only in an additional 45. An additional 20 patients were found to have less than 20 clinical units of free acid. In these groups there were three carcinomas of the stomach and ten polyps. In a group of 84 achlorhydric persons observed in a previous study five additional polyps were found. No carcinoma was encountered in 79 patients with pernicious anemia examined roentgenologically. Forty relatives of 20 patients with gastric carcinoma were examined, but no cancer was found. Of 40 patients with occult blood in the stool, 34 were submitted to roentgenologic study; no unsuspected cancer was found. Of 20 patients with hemoglobin values below 11.0 Gm., roentgenograms of the stomach were made on 10; none of these had carcinoma.

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132. Kaplan, H. S., and Rigler, L. G.: Pernicious Anemia and Susceptibility to Gastric Neoplasms, *J. Lab. & Clin. Med.* 32:644-653, 1947. Rigler, L. G., and Kaplan, H. S.: Pernicious Anemia and Tumors of the Stomach, *J. Nat. Cancer Inst.* 7:327-332, 1947.

133. Benedict, E. B.: Observations on Gastric Atrophy After Liver Therapy, *J. Nat. Cancer Inst.* 7:321-325, 1947.

134. State, D.; Varco, R. L., and Wangenstein, O. H.: An Attempt to Identify Likely Precursors of Gastric Cancer, *J. Nat. Cancer Inst.* 7:379-385, 1947.

An important study by Comfort, Kelsey and Berkson<sup>135</sup> disclosed that achlorhydria was present in 127 (45.8 per cent) of a series of 277 cases of gastric cancer in which gastric analysis (modified Ewald test) was performed two or more years before the cancer was diagnosed. In the 150 cases in which the gastric contents contained acid the mean free acid was 35.3 clinical units at an average of 11.2 years before the diagnosis of cancer was made. A subnormal gastric secretory activity was characteristic of these patients with precancerous lesions regardless of the decade of life in which the initial test meal was given and also at all intervals in the years before cancer was diagnosed, even being present for as long as twenty to twenty-five years and more before the cancer developed. The mean secretory activity of the 186 patients for whom gastric analysis was carried out at the time of the diagnosis of cancer as well as at the initial investigation decreased in the interval between the two analyses. The percentage of patients who had achlorhydria increased to 68.8, and the mean acidity value among those with acid diminished to 31.6 clinical units. The process responsible for the lowering of gastric acidity appears to have been progressive but selective, because the gastric acidity did not appreciably decrease in all cases.

*Cytologic Elements of Gastric Fluid.*—Examination of the cellular elements of gastric fluid obtained by aspiration of the fasting stomach was carried out by a technic first applied in the diagnosis of cancer of the female genital tract.<sup>136</sup> Among the 27 cases of cancer a false negative diagnosis was made in 10, a diagnosis of suspected cancer in 7 and a positive diagnosis in 10. Three of the 10 patients for whom cancer was not diagnosed were found to have scirrhous lesions; in 3 others the cells were poorly preserved. In the 110 cases without gastric cancer a false positive diagnosis was made in none and a diagnosis of suspected cancer in only 9.

*Metabolic Disturbances.*—Patients with gastric cancer have faulty hepatic glycogen formation, which can be corrected by the administration of an adrenal extract, according to Rhoads.<sup>137</sup> Application of the Kepler test for Addison's disease has yielded results in patients with gastric cancer which resemble more closely those seen in Addison's disease than those present in any other disorder of known origin. In addition, there is a high incidence of hypoproteinemia, with an impaired capacity for regeneration of plasma proteins.

*Diagnosis.*—Problems in the diagnosis of gastric carcinoma are re-

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135. Comfort, M. W.; Kelsey, M. P., and Berkson, J.: Gastric Acidity Before and After the Development of Carcinoma of the Stomach, J. Nat. Cancer Inst. 7:367-373. 1947.

136. Papanicolaou, G. N., and Cooper, W. A.: The Cytology of Gastric Fluid in the Diagnosis of Carcinoma of the Stomach, J. Nat. Cancer Inst. 7:358-359, 1947.

137. Rhoads, C. P.: Studies of Patients with Gastric Cancer, J. Nat. Cancer Inst. 7:333-336, 1947.



viewed by Golob.<sup>138</sup> Anglem<sup>139</sup> emphasizes the difficulty of early diagnosis. The average interval from the onset of symptoms to the first visit to a physician was nine months; the interval from the onset of symptoms to the establishment of diagnosis averaged seventeen months. It is to be noted that in 24 per cent of the cases the first roentgenogram failed to establish the diagnosis. Hudson and Alt,<sup>140</sup> on the basis of 60 cases studied between 1917 and 1945, found only slight improvement in diagnosis and in the surgical results.

In a study by Maimon and Palmer<sup>141</sup> the symptoms at the time of diagnosis were found to be of less than three months' duration in one fourth of the cases and of less than six months' duration in 53.7 per cent. Gastroscopy yielded the correct diagnosis in 84.6 per cent of the cases in which it was utilized. Roentgen examination provided the correct diagnosis in 91.8 per cent of the patients so examined. Attention is again directed to the need for prompt roentgenologic and gastroscopic study of patients with "dyspeptic" symptoms. In contrast to the preceding report, a trend toward earlier diagnosis is detected. Katsnelson<sup>142</sup> states that in Russia approximately 70,000 people die each year of cancer of the stomach. Present methods of diagnosis are reviewed, and the author reiterates the need for the thorough examination of all patients who have reached the so-called cancer age.

The importance of a competent roentgen examination of the stomach for all persons with digestive complaints, regardless of how mild they may appear, and for all those with predisposing diseases, such as pernicious anemia, in the early diagnosis of gastric cancer is emphasized by Crismer,<sup>143</sup> Dailey,<sup>144</sup> Templeton<sup>145</sup> and Giles.<sup>146</sup> A plan is presented

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138. Golob, M.: Gastric Carcinoma: Review of Errors in Diagnosis, *Am. J. Digest. Dis.* **13**:17-23, 1946.

139. Anglem, T. V.: Dyspepsia, Ulcer and Gastric Cancer, *New England J. Med.* **235**:322-325, 1946.

140. Hudson, P. B., and Alt, R.: Carcinoma of the Stomach, *Am. J. Surg.* **72**:202-211, 1946.

141. Maimon, S. N., and Palmer, W. L.: Gastric Carcinoma: Incidence and Diagnostic Procedures, *Surg., Gynec. & Obst.* **83**:572-574, 1946.

142. Katsnelson, S. M.: Recognition of Gastric Carcinoma, *Am. Rev. Soviet Med.* **4**:134-141, 1946.

143. Crismer, R.: Contribution a l'étude du diagnostic radioclinique précoce du cancer gastrique: Examen général de la question et presentation de deux cas personnels, *Rev. med. Liège* **2**:11-20, 1947.

144. Dailey, M. E.: The Role of Cancer-Prevention Clinics in the Detection of Early Gastric Cancer, *J. Nat. Cancer Inst.* **7**:375-377, 1947.

145. Templeton, F. E.: Gastric Carcinoma: Can an Increased Diagnostic Accuracy Greatly Improve Survival Rates?, *J. Nat. Cancer Inst.* **7**:385-386, 1947.

146. Giles, R. G.: Roentgenological Consideration of Gastro-Intestinal Disturbances with Special Reference to the Stomach and Duodenum, *South. M. J.* **39**:570-574, 1946.

for the utilization of mass fluoroscopic and roentgenologic studies as a means of discovering curable lesions.<sup>147</sup>

*GastroscoPy and Gastric Cancer.*—Moersch and Kirklin<sup>148</sup> reviewed 100 selected cases of carcinoma of the stomach in which the diagnosis proved difficult, for the purpose of evaluating the accuracy of the gastroscopic and roentgen examination. In 10 instances it was impossible to make a definite diagnosis gastroscopically because of inadequate visualization; the roentgenologist experienced difficulty in arriving at a definite diagnosis in 6 cases. The gastroscopist's interpretation proved to be wrong in 20 cases, whereas the roentgenologist's opinion was incorrect in 42 cases. The source of greatest error in gastroscopic diagnosis was in the differentiation of carcinoma from severe hypertrophic gastritis; the error from this source was made eleven times. The roentgenologist experienced the same difficulty in 10 instances, misinterpreting the carcinomatous process as gastritis. Five ulcers regarded as benign gastroscopically proved on histopathologic examination to be malignant; a similar error was made by the roentgenologist in 14 instances. Moersch and Kirklin conclude that histopathologic examination of the lesion remains the most accurate method of distinguishing between benign and malignant ulcer. However, the close collaboration of the gastroenterologist, roentgenologist and gastroscopist improves the likelihood of early correct diagnosis. In a later report, Moersch<sup>149</sup> concludes that gastroscopy is of value in the differential diagnosis between carcinoma and gastritis. It is not infallible, however, there being an incidence of error of approximately 10 per cent. Palpation of the stomach during gastroscopy may induce peristalsis and bring into view areas otherwise not visualized. Schlindler<sup>150</sup> found that gastroscopy and roentgen examination each yielded the correct diagnosis in 92.3 per cent and the incorrect diagnosis in 7.7 per cent.

*Coexistent Ulcer and Cancer.*—Three cases of coexistent benign ulcer and carcinoma are described by Yarnis.<sup>151</sup> The rarity of concurrent duodenal ulcer and gastric carcinoma is emphasized in a report by Fischer.

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147. Abrahamson, R. H., and Hinton, J. W.: Gastric Carcinoma: A Comparative Review of the Origin, Diagnosis and End-Results in Five Hundred and Eighty-Three Patients, *Surg., Gynec. & Obst.* **84**:481-490, 1947.

148. Moersch, H. J., and Kirklin, B. R.: Gastroscopy and Its Relationship to Roentgenology in the Diagnosis of Carcinoma of the Stomach, *Gastroenterology* **7**:285-293, 1946.

149. Moersch, H. J.: The Gastroscopic Differentiation of Gastritis from Carcinoma of the Stomach, *Gastroenterology* **8**:284-292, 1947.

150. Schlindler, R.: What Does Gastroscopy Offer in the Early Diagnosis of Cancer of the Stomach?, *California Med.* **66**:110-116, 1947.

151. Yarnis, H.: Coexisting Ulcer and Cancer of the Stomach, *S. Clin. North America* **27**:299-307, 1947.

Clagett and McDonald,<sup>152</sup> who found only 48 proved cases in a series of 13,000 cases of carcinomas of the stomach. The age and sex incidence were approximately the same as in carcinoma of the stomach in general. The survival rate in this group of cases was considerably higher than that usually found in carcinoma.

*"Carcinomatous Transformation."*—On the basis of a pathologic study of surgically resected specimens, Koszewski<sup>153</sup> concludes that the incidence of carcinomatous transformation from ulcer is 14.63 per cent, as compared with an incidence of 3.0 per cent in necropsy studies. The author considers the real incidence to be between these two figures. The reviewers disagree with these figures and conclusions because there is no pathognomonic sign to indicate that a given ulcerating carcinoma began as a benign ulcer and underwent "malignant degeneration or transformation." Peptic activity may produce in a neoplasm the architecture of a benign ulcer and all the alleged criteria of preexisting benign ulcer.

*Unusual Clinical Features.*—Carcinoma in a boy aged 15, treated by subtotal gastrectomy of the Polya type, was found to be an ulcerated epithelioma with multiple metastases to lymph nodes.<sup>154</sup> The boy was alive six months after operation. An analysis of cancer of the stomach in 92 children and adolescents indicated that the condition is extremely rare in persons under 20 years of age but ceases to be exceptional in persons over this age. Epithelioma was present in 69 of the 92 patients, sarcoma in 17 and Krukenberg's tumor in 6. The symptomatology in children did not differ from that in the adult.

Three adenocarcinomas of the stomach invading the gastric wall simulated roentgenologically an extramucosal tumor.<sup>155</sup>

Boyce<sup>156</sup> reports a series of 36 perforating neoplasms, an incidence of approximately 2 per cent. Thirty-one of the patients were males and 5 females.

Acanthosis nigricans in a patient with an ulcerating cancer of the gastric antrum apparently regressed after removal of the neoplasm.<sup>157</sup>

*Surgical Treatment and Results.*—The numerous statistical analyses of the results of surgical treatment for gastric cancer are rather con-

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152. Fischer, A.; Clagett, O. T., and McDonald, J. R.: Coexistent Duodenal Ulcer and Gastric Malignancy, *Surgery* 21:168-174, 1947.

153. Koszewski, von B. J.: Zur Frage der Häufigkeit des Ulkuskarzinoms des Magens, *Gastroenterologia* 71:210-232, 1946.

154. Funck-Brentano, and Tubiana, R.: Cancer of Stomach in First Two Decades of Life, *Semaine d'hôp. Paris* 23:1171-1173, 1947.

155. Lowman, R. M.; Shapiro, R. and Kushlan, S. D.: Extramucosal Tumors Simulated by Gastric Carcinoma, *Am. J. Roentgenol.* 57:726-735, 1947.

156. Boyce, F. F.: Perforated Gastric Malignancy, *Surg., Gynec. & Obst.* 83:718-724, 1946.

157. Warmoes, F., and Goubau, P.: Un cas d'acanthosis nigricans en relation avec un cancer a l'estomac, *Acta gastroenterol. belg.* 9:219-222, 1946.

fusing, for there are different ways of approaching the problem; varying standards are used, and particular aspects of the subject are emphasized. To the reviewers there seems to be a slight trend toward earlier operation, a definite trend toward a higher resectability rate, a lower mortality rate and longer postoperative survivals in a higher percentage of the patients.

Schindler,<sup>158</sup> in a series of 107 patients with resected carcinomas, found that only 7 survived for three years. In 6 of these the tumors were sharply localized, and of types I and II in the Borrmann classification; one was an infiltrative lesion. After five years only 4 patients were known to be alive.

Laparotomy performed in 83.5 per cent of 466 patients at the University of Chicago<sup>159</sup> resulted in a resectability rate of 43.5 per cent, with a survival rate of 32.2 per cent. Among 203 patients who underwent resection the survival rate was 73.7 per cent. The mortality for gastric resection of all types was 26.1 per cent for the seventeen years. Peritonitis was the chief cause of postoperative death. No residual carcinoma was demonstrated at autopsy in 25 per cent of the patients who died from gastric resection.

Harnett<sup>160</sup> reviews observations on 1,405 patients with cancer of the stomach treated in London hospitals during 1938 and 1939. The operability rate was 49.2 per cent and the resectability rate 17.3 per cent. The operative mortality for all radical operations averaged 32.9 per cent, ranging from 25.4 per cent for the Polya method of partial gastrectomy to 90 per cent for total gastrectomy. The survival rate for all radical operations averaged 23.1 per cent in traced cases after operative fatalities were excluded. Resection before the lymph nodes were involved resulted in a 60 to 63 per cent normal expectation of life over a five year period. After involvement of the lymph nodes, resection resulted in only a 40 to 43 per cent normal life expectancy. The average for all patients, including those not treated, was 27.4 per cent of normal. Women had the best survival rate.

In a series of 419 patients the lesion was found inoperable in 48.2 per cent.<sup>161</sup> Exploratory laparotomy and biopsy were done in 19.4 per cent, a palliative operation in 8.3 per cent and a partial gastrectomy in 24.1

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158. Schindler, R.: Relative Surgical Curability of Certain Gross Types of Gastric Carcinoma, *Surg., Gynec. & Obst.* **83**:453-461, 1946.

159. Maimon, S. N., and Palmer, W. L.: Gastric Cancer: Laparotomy, Resectability, and Mortality, *Surg., Gynec. & Obst.* **83**:480-484, 1946.

160. Harnett, W. L.: Statistical Study of 1405 Cases of Cancer of the Stomach, *Brit. J. Surg.* **34**:379-385, 1947.

161. Marshall, S. F., and Welch, M. L.: Carcinoma of the Stomach: Rate of Operability, *S. Clin. North America* **27**:631-635, 1947.

per cent. Eliason and Witmer<sup>162</sup> review 149 cases observed from 1929 to 1934; 64 per cent of the patients were males, with 81 per cent between the ages of 40 and 70. The surgeon was consulted three months or longer after the onset of symptoms in 75 per cent of the cases and one year or more in 42 per cent. In only 52 cases was the condition operable; there were three five year cures.

Pack<sup>163</sup> points out that improvement in end results may be attributed to a greater awareness on the part of the general public, improved facilities for the diagnosis of cancer, a wider application of surgical resection by an increased number of surgeons and, finally, the introduction of extremely radical surgical procedures of three types, namely, removal of the organs adjacent to the stomach involved by contiguity, total gastrectomy when the cancer involves the major part of the stomach and trans-thoracic, transdiaphragmatic cardiectomy for cancers involving the cardia. Better appreciation of proper preoperative and postoperative care of the patient are important additional factors.

Improved results are indicated in a series of papers dealing with total gastrectomy. Marshall and Brown<sup>164</sup> report a surgical mortality of 43.4 per cent during the period 1929 to 1942 and of 16.3 per cent from 1942 to January 1947. Eighty-nine patients, 88 with neoplasm, underwent a complete gastrectomy,<sup>165</sup> with a mortality of 29.1 per cent. The mortality during the last three years and nine months of the study was 16.3 per cent. Twelve patients have survived the operation for three or more years. Of 20 patients subjected to total gastrectomy by Longmire,<sup>166</sup> 2 died; 7 patients survived more than a year and resumed their previous occupations. In a series of 98 radical resections for gastric cancer Ischchenko<sup>167</sup> found a mortality of 13.2 per cent. Wahren<sup>168</sup> performed 9 total resections, and there were no deaths. Buschmann<sup>169</sup> reports an advanced adenocarcinoma with local metastasis successfully treated by combined gastrectomy and colectomy.

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162. Eliason, E., and Witmer, R. H.: Surgical Aspects of Carcinoma of the Stomach, *Am. J. Surg.* **72**:679-682, 1946.

163. Pack, G. T.: The Radical Surgical Treatment of Gastric Cancer, *J. Nat. Cancer Inst.* **7**:337-344, 1947.

164. Marshall, S. F., and Brown, L. H.: Total Gastrectomy, *S. Clin. North America* **27**:621-635, 1947.

165. Smith, F. H.: Total Gastrectomy: Report of Eighty-nine Cases, *Surg., Gynec. & Obst.* **84**:42-408, 1947.

166. Longmire, W. P.: Total Gastrectomy for Carcinoma of the Stomach, *Surg., Gynec. & Obst.* **84**:21-30, 1947.

167. Ischchenko, I. N.: Gastric Resection for Cancer, *Am. Rev. Soviet Med.* **4**:130-134, 1946.

168. Wahren, H.: Total Resection of the Carcinomatous Stomach, *Acta chir. Scandinav.* **95**:193-204, 1947.

169. Buschmann, T. W.: Advanced Carcinoma of Stomach Requiring Combined Gastrectomy and Colectomy, *Northwest Med.* **46**:126-127, 1947.

Neibling and Walters<sup>170</sup> report a total gastrectomy with esophagoduodenal anastomosis for diffuse linitis plastica of the stomach in a 65 year old woman. Apart from a minimal phlebitis on the seventeenth day, the postoperative course was uneventful and the patient made a good recovery. Prior to 1945, three such operations were performed at the Mayo Clinic. The first 2 patients died while still in the hospital. The third patient and 3 others operated on since 1945, included the one just mentioned, have survived.

Allison<sup>171</sup> describes a technic for palliative esophagojejunostomy in the management of irremovable carcinoma of the cardia.

#### PEPTIC ULCER

*Experimental Observations.*—According to LeVeen,<sup>172</sup> the effect of acids is to enhance the activity of pepsin rather than to produce ulceration by itself. Irrigations of the terminal end of the ileum of the dog with hydrochloric acid at a  $p_H$  of 1.5 and a temperature of 40 C. produced a brownish discoloration of the mucosal surface due to precipitation of mucus, but no ulcers developed. Petechial hemorrhage, superficial ulceration and mucosal congestion occurred after irrigation with 1 per cent solution of pepsin at a  $p_H$  1.5 and a temperature of 30 C. However, when pepsin activity was increased, a perforated ulcer 1.4 cm. in diameter developed. In general, ulcers formed more readily with solutions of increasing acidity. The secretion of mucus was stimulated by irrigations with acid solutions. Spasm of the bowel wall, by reducing the exposed surface area and increasing the secretion of mucus, apparently served as a protection from ulceration. Mucus presented a protective barrier, as evidenced by the fact that ulcers formed only in the area in which the stream of irrigation kept the mucosa free of mucus.

Various living tissues, including omentum, intestine, liver, gallbladder, pancreas, spleen, kidney, lung, cartilage, skin and the gastric wall itself, were implanted in the lumen of the stomach or maintained in prolonged surface contact with gastric secretion.<sup>173</sup> Virtually all the tissues and organs so tested underwent digestion; those most rapidly digested were the external coats of the intestines, appendix and gallbladder, and those most resistant were fibrous connective tissue, skin and intestinal mucosa. The one tissue which seemed to be resistant to ordinary digestion

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170. Neibling, H. A., and Walters, W.: Total Gastrectomy with Esophagoduodenal Anastomosis, Proc. Staff Meet., Mayo Clin. **21**:449-453, 1946.

171. Allison, P. R.: Oesophago-Jejunostomy for Irremovable Carcinoma of the Cardia, Thorax **1**:239-246, 1946.

172. LeVeen, H. H.: Chemical, Physiological, and Pathological Observations on the Role of Pepsin and Hydrochloric Acid in the Production of Experimental Ulcers, Gastroenterology **8**:648-661, 1947.

173. Price, P. B., and Lee, T. F.: The Gastric Digestion of Living Tissue, Surg., Gynec. & Obst. **83**:61-72, 1946.

was gastric epithelium. Tissues undergoing digestion manifested different types and degrees of reaction. Serous surfaces became acutely inflamed, with rapid leukocytic infiltration and necrosis. The capsules of liver, spleen and kidney responded with excessive amounts of fibrosis. Epidermal surfaces slowly eroded, with little or no cellular reaction. Active fibrosis and granulation tissue served to produce resistance to digestion. Once tissues were covered with proliferating gastric epithelium, they appeared to be safe from further corrosive action.

Twenty-four hours after ligation of the single artery and vein supplying the antrum, a single, penetrating 5 mm. ulcer developed in the center of the antrum in 10 of 18 rats.<sup>174</sup> Two perforations were observed. Unilateral ligation of the fundic vessels in 20 rats resulted in an intense purplish congestion of the mucosa; ulcer did not develop in 12 of the rats after twenty-four hours, but it did develop in 1 of 8 rats after forty-eight hours. Bilateral ligation of the fundic vessels produced mottled red to brown blotches in the mucosa. Twenty-four hours after ligation 5 of 8 animals had multiple ulcers in both halves of the fundus. Lack of anastomotic blood supply is postulated as the cause of these ulcers. Some rats were kept for eight to sixteen days after ligation, and all survived. Various stages of repair were observed; the fundic lesions showed more advanced healing, probably because of better collateral circulation.

Harris and others<sup>175</sup> induced ulcers in the forestomach of rats recovering from vitamin A deficiency and receiving 2, 30 and 300 units of vitamin A daily, rats recovering from vitamin B<sub>6</sub> deficiency and receiving suboptimal amounts of pyridoxine and rats recovering from a deficiency of essential fatty acids and receiving 20 mg. of linoleate daily. Ulcers occurred only in the recovery period. Tocopherol fed daily protected the rats against the formation of ulcers, whereas injected tocopherol phosphate did not.

Ulcers are provoked more readily in dogs and rabbits subjected to experimental burns when histamine is given.<sup>176</sup> Ulcers occurred in 2 of 11 animals subjected to burns alone (18.2 per cent), whereas in all the 14 dogs burned in addition to being exposed to histamine, erosion or ulcer was present. Friesen and Wangensteen<sup>177</sup> present evidence that gastro-

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174. Berg, B. N.: Gastric Ulcers Produced Experimentally by Vascular Ligation, *Arch. Surg.* **54**:58-66 (Jan.) 1947.

175. Harris, P. L.; Hove, E. L.; Mellott, M., and Hickman, K.: Dietary Production of Gastric Ulcers in Rats and Prevention by Tocopherol Administration, *Proc. Soc. Exper. Biol. & Med.* **64**:273-277, 1947.

176. Friesen, S. R., and Wangensteen, O. H.: Experimental Burns Accompanied by Histamine Administration Abets the Ulcer Diathesis, *Proc. Soc. Exper. Biol. & Med.* **63**:245-248, 1946.

177. Friesen, S. R., and Wangensteen, O. H.: Role of Hemoconcentration in Production of Gastric and Duodenal Ulcer Following Experimental Burns, *Proc. Soc. Exper. Biol. & Med.* **64**:81-85, 1947.

intestinal abnormality following burns, even when accompanied with administration of histamine, may be prevented by avoidance of hemoconcentration. Babkin and Lawson<sup>178</sup> successfully performed a gastroduodenoduodenostomy in a dog which remained in good health for more than a year. The fasting stomach always contained an average of 100 cc. of alkaline, bile-stained fluid; trypsin was present in high concentration. The absence of ulceration was attributed to the lowered acidity and peptic activity of the gastric contents.

*Radiation.*—Five patients with a variety of malignant lesions not involving the stomach received from 5,000 to more than 6,000 r, administered through two gastric portals, anterior and posterior, over a period of almost one month.<sup>179</sup> Diffuse inflammation of the stomach, erosions and ulceration were observed in all cases.

Betz<sup>180</sup> irradiated the abdominal wall of 29 rabbits with doses varying from 1,000 to 3,000 r and produced both diffuse and localized lesions in the mucosa. The diffuse lesions consisted of a direct alteration of the glandular elements in the following order of sensitivity: the superficial epithelium, the pyloric glands, the chief cells and the parietal cells. The localized lesions consisted of hemorrhages and ulcers. The small subepithelial hemorrhages disappeared rapidly; the localized hemorrhagic infiltration of the mucosa, found almost exclusively at the pyloric end or in the lesser curvature, was transformed into ulcers. The hemorrhagic necroses were secondary to lesions of the capillaries. The lesions were acute and were directly related to the amount of radiation administered. The animals receiving 2,400 r died after eight to ten hours, and the animals receiving 1,500 r died between the fifteenth and the twentieth hour. In 1 animal killed four hours after a dose of 3,000 r there was no macroscopic alteration. Three animals receiving 2,400 r had severe lesions; in 2 the lesions perforated. Of 2 animals receiving 1,800 r, 1 had no lesion after seven hours, and the other had superficial ulcers after nine hours. Of 20 animals given 1,500 r and killed within nine hours to nine days, 5 showed no lesion, 5 had hemorrhages and 10 had ulcers. In 1 animal receiving 1,200 r and in 2 receiving 1,000 r no abnormality was found.

*Treatment of Experimental Ulcer.*—Seven dogs were given 30 mg. of histamine in beeswax, intramuscularly, daily.<sup>181</sup> In 2 of the animals,

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178. Babkin, B. P., and Lawson, R. N.: Gastroduodenoduodenostomy, *Acta Med. Scandinav.* (supp. 196) 128:308-321, 1947.

179. Brick, I. B.: Radiation Effects on the Human Stomach, *Rev. Gastroenterol.* 13:363-370, 1946.

180. Betz, H.: Contribution a l'étude de l'ulcère gastrique: I. Sur la production d'ulcères gastriques par irradiation abdominale chez le lapin, *Rev. belge sc. méd.* 17:121-154, 1946.

181. Fast, J.; Friesen, S. R., and Wangenstein, O. H.: The Sippy Regimen Protects Against the Histamine-Provoked Ulcer, *Gastroenterology* 8:662-664, 1947.



serving as controls, posterior duodenal ulcers were found after thirty-four and thirty-nine days. The five remaining dogs, subjected to gastrostomy, received a modified Sippy diet consisting mainly of milk and an alkaline mixture of 1.3 Gm. of sodium bicarbonate and 0.6 Gm. of bismuth subcarbonate alternately every hour from 8:00 a.m. to 7:00 p.m. The gastric contents were removed at 9:00 p.m. and 200 cc. of milk instilled. The diet was supplemented with horse meat, liver and vitamins after the first week. No ulceration or erosion was found in 4 dogs killed on the forty-first day.

"Benadryl hydrochloride" (N.N.R.) given to dogs with Pavlov or Heidenhain pouches by oral, subcutaneous and intravenous routes failed to alter the gastric secretory response to histamine and to protect against the histamine-provoked ulcer.<sup>182</sup> When given alone, it produced neither an increase nor a decrease in the level of gastric secretion in fasting dogs. The results indicate that "benadryl hydrochloride" is not a specific antagonist of histamine. Similar observations were made by Crane and others<sup>183</sup> on 16 adult albino guinea pigs given daily injections of 0.1 cc. of a histamine suspension in beeswax and oil (containing 100 mg. of histamine base per cubic centimeter) for eleven days. Eight of the animals were then given "benadryl hydrochloride" in quantities of 135 mg. per kilogram of body weight daily, administered in divided doses in sterile water intraperitoneally. Gastric ulcers developed in 5 of the benadryl-treated animals, perforation occurring in 4. Six of the control group showed ulcers, of which four had perforated.

"Benadryl hydrochloride" given in doses sufficiently large to produce drowsiness had no influence on gastric motility or acidity in 6 patients.<sup>184</sup> Clinical improvement was observed in 5 of the group, but the authors correctly point out that peptic ulceration, with its characteristic remissions, is peculiarly unsuited for therapeutic trials assessed on a purely clinical basis.

Evaluation of various therapeutic agents used in the management of peptic ulcer was made to test their ability to protect the rumen of rats from ulceration after ligation of the pylorus.<sup>185</sup> Sodium dodecyl sulfate and colloidal aluminum hydroxide used in combination offered complete protection. When given singly, these preparations prevented ulcers in 80 per cent of the rats. Other agents in order of effectiveness were

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182. Friesen, S. R.; Baronofsky, I. D., and Wangenstein, O. H.: Benadryl Fails to Protect Against the Histamine-Provoked Ulcer, *Proc. Soc. Exper. Biol. & Med.* **63**:23-25, 1946.

183. Crane, J. T.; Lindsay, S., and Dailey, M. E.: An Attempt to Prevent Histamine-Induced Ulcers in Guinea Pigs with Benadryl, *Am. J. Digest. Dis.* **14**:56-57, 1947.

184. Kay, A. W.; Scott, L. D. W., and Smith, W. E.: Observations on Use of Benadryl in Duodenal Ulcer, *Glasgow M. J.* **28**:145-148, 1947.

185. Shay, H.; Komarov, S. A.; Siplet, H., and Gruenstein, M.: An Evaluation of Some Antacid and Antipeptic Agents in the Prevention of Gastric Ulceration in the Rat, *Am. J. Digest. Dis.* **14**:99-103, 1947.

sodium aluminum trisilicate, magnesium oxide, dibasic aluminum aminoacetate, magnesium trisilicate and sodium bicarbonate.

After ligation of the pylorus, 480 ulcers were produced in 22 starved rats of a control series, whereas no ulcers developed in 20 vagotomized rats after ligation of the pylorus.<sup>186</sup> Ulcers occurring after pyloric ligation in rats were apparently prevented by the intravenous administration of 50 mg. of a neutral extract prepared from normal human urine.<sup>187</sup>

A method is described which utilizes a rat preparation for the assay of so-called anti-gastric-ulcer factors.<sup>188</sup> After a fasting period, lengthened with the age of the animal, the pylorus is ligated and fasting continued. Gastric juice accumulates in the stomach, and ulceration of the rumen ensues. In young rats extensive ulceration occurs in seven to nine hours, while in older rats a longer postoperative period is required. A proposed method of recording consists in a grading which ranges from "clear" for animals with no ulceration to 4 plus for those with the most extensive ulceration. Factors affecting the assay, such as technic of operation, age and sex of the animal and period of fast, are discussed. The gastric ulcers are attributed to peptic activity. Among 47 Sprague-Dawley albino male rats treated through various parenteral routes with enterogastrone in doses ranging from 20 to 500 mg. per kilogram for periods of one to thirty days rumenal ulcers developed in all but 1.<sup>189</sup> There was no correlation between the size of the dose, the length of treatment and the number of ulcers.

*Mechanism of Ulcer Pain.*—Bonney and Pickering<sup>190</sup> present highly significant data on the mechanism of pain in peptic ulcer. In 55 cases of gastric, duodenal or anastomotic ulcer and in a small number of cases of gastric cancer they found that ulcer pain was relieved by aspiration of the stomach and could be induced by reintroduction of the gastric contents; pain was not produced if the contents were neutralized prior to injection. Pain nearly always recurred when the gastric contents attained:

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186. Harkins, H. N.: Prevention of Pyloric Ligation-Induced Ulcers of the Gastric Rumen of Rats by Trans-Abdominal Vagotomy: Preliminary Report, Bull. Johns Hopkins Hosp. **80**:174-176, 1946.

187. Wick, A. N.; Irish, A. J.; Pauls, F., and MacKay, E.: Preparation of an Anti-Ulcer Factor from Human Urine, Proc. Exper. Biol. & Med. **64**:40-44, 1947.

188. Pauls, F.; Wick, A. N., and MacKay, E. M.: An Assay Method for Anti-Ulcer Substances, Gastroenterology **8**:774-782, 1947.

189. Morris, C. R.; Grossman, M. I., and Ivy, A. C.: Failure of "Enterogastrone" to Prevent Rumenal Ulcers in the Shay Rat, Am. J. Physiol. **148**:382-386, 1947.

190. Bonney, G. L. W., and Pickering, G. W.: Observations on the Mechanism of Pain in Ulcer of the Stomach and Duodenum: I. The Nature of the Stimulus. Clin. Sc. **6**:65-89, 1946.

a certain degree of acidity for a sufficient time and was nearly always absent or subsiding when gastric acidity fell below a certain level for a sufficient time. In the pain-free periods and in normal subjects the introduction of acid did not induce pain. The threshold of acidity necessary to evoke pain varied greatly from one patient to another. In general, duodenal ulcer manifested the highest threshold and anastomotic ulcer the lowest, with gastric ulcer intermediate; in some cases of gastric carcinoma the threshold was still lower than that found in peptic ulcer. Thus, the  $p_H$  necessary to evoke pain was about 1.5 for patients with duodenal and gastric ulcer and as low as 2.75 in anastomotic ulcer. Intra-gastric pressure during pain induced by acid solutions usually was slightly lower than that observed in the absence of pain. Roentgenologic examination during pain revealed no localized contractions of the stomach or duodenum that were not present when pain was absent.

Bonney and Pickering also studied the time relations for the onset of pain when acid is applied to an experimentally produced ulcer of the skin.<sup>191</sup> The time required for the induction of pain by acid and for its relief by neutralization was found to be much shorter than that observed in cases of peptic ulcer. The time was slightly prolonged by covering the ulcer with a thin film of mucus. When, however, the skin ulcer was protected by a scab, the time relations were greatly prolonged and were then of the same order of magnitude as that observed in peptic ulcer. It seems, therefore, that the time relations of pain in the presence of peptic ulcer are related to the chemical stimulation of nerve endings situated in the ulcer crater and separated from the cavity of the stomach or duodenum by a layer of inert material. These findings confirm the previously reported observations of Palmer that pain in peptic ulcer results from the exposure of a defective mucus membrane to a sufficient concentration of hydrogen ions and that it is not due to general or local contraction of the stomach or duodenum.

*General Observations.*—Current concepts of gastroduodenal ulcer are reviewed by Eusterman.<sup>192</sup> Ivy,<sup>193</sup> in a stimulating discussion of the ulcer problem, points out that peptic ulcer develops in approximately 1,500,000 persons in the United States above the age of 30 during a period of ten years and that the disease will develop in 10 per cent of the population at some time in their lives. The predominance of duodenal ulcer and its greater incidence in males have not been explained. The postoperative

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191. Bonney, G. L. W., and Pickering, G. W.: Observations on the Mechanism of Pain in Ulcer of the Stomach and Duodenum: II. The Location of the Pain Nerve Endings, *Clin. Sci.* 6:91-111, 1946.

192. Eusterman, G. B.: Newer Phases of Gastroduodenal Ulcer, *Gastroenterology* 8:575-585, 1947.

193. Ivy, A. C.: The Problem of Peptic Ulcer, *J.A.M.A.* 132:1053-1059. (Dec. 28) 1946.

gastrojejunal ulcer, caused chiefly by the action of acid on the jejunal mucosa, is the only ulcer occurring in man that has been reproduced experimentally. Ivy further states that adequate proof does not exist for the propositions that the patient with peptic ulcer has a characteristic personality pattern, that certain emotional states regularly induce gastric hyperactivity and that a state of gastric hyperactivity alone can cause peptic ulcer. The development of some therapeutically practical and innocuous method for increasing the resistance of the gastric, duodenal and jejunal mucosa to injury and for completely blocking the parietal cell is regarded as the most promising investigative approach to the ulcer problem.

*Incidence.*—Ulcer in South Australia is reviewed by Linn.<sup>194</sup> A marked increase in the incidence occurred in Belgium during the war years, with a particularly sharp increase in the frequency of gastric ulcer.<sup>195</sup> Knutsen and Selvaag<sup>196</sup> investigated the incidence of peptic ulcer during the year 1942 in a typical Norwegian town of 25,830 persons. Ulcer was found in 537 persons, or 2.08 per cent of the total population, and 2.45 per cent of the population above the age of 15. The ratio of men to women was 2.49 to 1. The ratio of gastric ulcer to duodenal ulcer was 1 to 1.85. Gastric ulcer was more frequent in the age groups above 50 and relatively more common among women than among men. There were 10 multiple ulcers of the stomach in a series of 200 roentgenologically demonstrated craters.<sup>197</sup>

*Psychosomatic Relationships.*—Crohn<sup>198</sup> reports several interesting cases in which recurrence of peptic ulcer and even perforation followed severe psychic trauma. Gainsborough and Slater<sup>199</sup> investigated a group of 130 men and 32 women with peptic ulcer psychiatrically and followed them after treatment for periods up to three years. The chief characteristics of the male patients were their energetic dispositions, tendency to anxiety, irritability, obsessionality and hypochondriasis. Their occupations and their school and work records revealed that the patients were good workers and somewhat superior to the average. Actual neurosis

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194. Linn, H. W.: An Analysis of Peptic Ulcer in South Australia, Based on a Study of 1,027 Case Reports, *M. J. Australia* 2:649-658, 1946.

195. DeWitt, J.: L'influence de la guerre mondiale sur la fréquence et la localisation des ulcères gastroduodénaux, *Acta gastro-enterol. belg.* 9:396-406, 1946.

196. Knutsen, B., and Selvaag, O.: The Incidence of Peptic Ulcer, *Acta med. Scandinav. (suppl. 196)* 128:341-360, 1947.

197. DeBusscher, G.: A propos de quelques ulcères multiples de l'estomac en pleine période de guerre, *Bruxelles med.* 26:939-943, 1946.

198. Crohn, B. B.: Peptic Ulcer as a Psychosomatic Disease, *S. Clin. North America*. 27:309-314, 1947.

199. Gainsborough, H., and Slater, E.: A Study of Peptic Ulcer, *Brit. M. J.* 2:253-258, 1946.

was uncommon, but the rate was somewhat higher among the women than among the men. The stresses to which the patients were exposed prior to their illness were principally those inseparable from ordinary life today. Unusual psychologic situations and patterns were infrequent. Failure in healing of the ulcer was not encountered, but relapses occurred in about one third within four months after their return to work. Cathcart<sup>200</sup> emphasizes the dominant role of deep-seated emotional conflicts in the production of peptic ulcer, which is in accordance with the theory of Alexander that the patient with ulcer meets a strong tendency toward dependency by overstriving in the direction of independence and self sufficiency. Peygrallo<sup>201</sup> likewise is impressed with the role of psychic factors in the pathogenesis of peptic ulcer.

Moses<sup>202</sup> believes that a high alpha index of the electroencephalogram is associated with passive, dependent, receptive trends whereas a low alpha index is usually associated with a consistent, well directed, freely indulged drive to activity. A previous investigation of patients with ulcer revealed that 70 per cent manifested a dominant alpha index, as contrasted with a 20 per cent incidence in normal persons. In a further study of 25 patients with peptic ulcer, characterized by pronounced feelings of insecurity associated with strong passive dependent traits, 76 per cent were found to fall into the dominant alpha group.

On the other hand, in a study in an Army General Hospital in Hawaii Radloff<sup>203</sup> noted that ulcers rarely developed in psychoneurotic soldiers with gastrointestinal complaints and that they rarely gave a history compatible with the diagnosis of ulcer. Vomiting was infrequent in patients with ulcer and common in those diagnosed as psychoneurotic. Routine medical management produced complete symptomatic relief in seven to ten days. Massive hemorrhage responded well to transfusions and early feeding. No fatalities were recorded.

Steiner<sup>204</sup> found no disease of the stomach among Okinawans except ulcer; the lesions were acute and were thought to be related to the psychosomatic stress occasioned by the bombing and invasion of the island.

The reviewers admit that to them the role of emotional factors in the production of peptic ulcer and in its recurrence still is an enigma. They are inclined to accept the evidence that in many patients, at least, such

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200. Cathcart, J. P. S.: The Role of the Emotions in the Production of Gastro-Intestinal Disturbances, *Canad. M. A. J.* **55**:465-470, 1946.

201. Peygrallo, R. A.: Componentes psíquicos de la úlcera gastro-duodenal, *An. de cir.* **11**:182-193, 1946.

202. Moses, L.: Psychodynamic and Electroencephalographic Factors in Duodenal Ulcer, *Psychosom. Med.* **8**:405-409, 1946.

203. Radloff, F. F.: Observations on Five Hundred and Forty-Three Cases of Peptic Ulcer, *Gastroenterology* **8**:343-347, 1947.

204. Steiner, P. E.: Necropsies on Okinawans: Anatomic and Pathologic Observations, *Arch. Path.* **42**:359-380 (Oct.) 1946.

factors are present and are sufficiently important to produce either an acute ulcer or a recurrence of a chronic lesion. It is also possible that entirely different mechanisms may be operative in other patients. Furthermore, the reviewers are skeptical of any specificity in the psychodynamic pattern.

*Allergy.*—Moutier<sup>205</sup> regards ulcer of the stomach as a disease of sensitization similar to other allergic syndromes such as eczema and urticaria but does not offer convincing evidence.

*Gastric Secretion.*—Caffeine-stimulated gastric secretion was measured in 20 patients with duodenal ulcer in remission, in 25 patients with active duodenal ulcer and in 10 normal persons.<sup>206</sup> The normal persons secreted an average total of 363 mg. of hydrochloric acid, the patients with ulcer in remission 361 mg. and the patients with active duodenal ulcer an average of 957 mg. The average concentration of hydrochloric acid in the normal persons was 86 mg. per hundred cubic centimeters; in patients with ulcer in remission it was 162 mg. and in patients with active duodenal ulcer 214 mg., or 149 per cent over that of the normal persons.

Sandweiss and his associates<sup>207</sup> studied the nocturnal secretion both in normal persons and in patients with uncomplicated duodenal ulcer; secretion was found to be continuous in both groups. When periodic aspirations were performed during the night, a greater volume was obtained from patients with duodenal ulcer than from normal persons. There was no statistically significant difference in the volume or in the total output of acid between the two groups when continuous aspirations were done. Studies made under the same conditions indicated that the curves of acid concentration vary considerably from one person to another, both normal and ulcer bearing, and also in the same persons on different nights. Sandweiss concludes that there is no difference between normal subjects and patients with uncomplicated duodenal ulcer as regards the volume and acidity of the gastric juice secreted during the night.

Other authors<sup>208</sup> have not been able to confirm the results of Sand-

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205. Moutier, F.: Interprétation allergique de l'ulcère gastro-duodéal basée sur ses caractères cliniques (douleurs tardives) et anatomiques, *Arch. d. mal. de l'app. digestif* **35**:273-284, 1946.

206. Musick, V. H.; Avey, H. T.; Hopps, H. C., and Hellbaum, A. A.: Gastric Secretion in Duodenal Ulcer in Remission-Response to the Caffeine Test Meal, *Gastroenterology* **7**:332-339, 1946.

207. Sandweiss, D. J.; Friedman, M. D. F.; Sugarman, M.D., and Podolsky, H. M.: Nocturnal Gastric Secretion: II. Studies on Normal Subjects and Patients with Duodenal Ulcer, *Gastroenterology* **7**:38-54, 1946.

208. Levin, E.; Hamann, A., and Palmer, W. L.: The Effect of Radiation Therapy on the Nocturnal Gastric Secretion in Patients with Duodenal Ulcer, *Gastroenterology* **8**:565-574, 1947.

weiss, whereas they have confirmed in essence those of Musick and others.<sup>206</sup>

The nocturnal gastric secretion was measured in 28 patients with duodenal ulcer.<sup>208</sup> The volume varied from 550 to 1,750 cc., with an average of 1,110 cc. The free acidity ranged from 18 to 122 clinical units, averaging 62. Nine of the patients were studied during the course of radiation therapy directed at the body and fundus of the stomach. Some reduction in the volume and in the free acidity was noted in 7; an increase was observed in 2 cases. Fifteen patients were studied at varying intervals after the completion of radiation therapy. Fourteen of these showed a decrease in volume, with an average reduction of 47 per cent. Thirteen patients exhibited complete anacidity in the nocturnal secretion; a considerable reduction in acidity occurred in the 2 remaining cases. A reduction in the secretory response to histamine stimulation was also noted in the 15 patients.

*Ascorbic Acid.*—Determinations of fasting plasma vitamin C levels and of the levels at one, two and three hours after a test dose of 1 Gm. of ascorbic acid in 13 patients with active peptic ulcer, in 7 with active hemorrhage, in 10 with asymptomatic ulcers under treatment and in 25 control patients disclosed that those with active ulcer manifested lowered initial levels, with flatter curves, after the test dose.<sup>209</sup> Patients with active ulcer and hemorrhage had the lowest levels. No appreciable diminution of the plasma vitamin C was found in the convalescing group. Statistical analysis of the data by the "t" test indicated significant differences between the control group and the patients having active and bleeding ulcers. It is concluded that vitamin C should be added to or included in the diets of patients with peptic ulcer.

*Diagnostic Considerations.*—Brown and Harper<sup>210</sup> recommend roentgen examination of the stomach and duodenum in the right lateral horizontal position as well as in the routine posteroanterior position for the diagnosis of duodenal ulcer.

Kay<sup>211</sup> reports rather unusual results in the diagnosis of active duodenal ulcer from testing, with a gastrogram, gastric motility in response to the ingestion of cold water. The test is based on the observation of Carlson (1916) that the ingestion of cold water inhibits gastric contractions for approximately five minutes and on that of Anderson (1943)

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209. Crescenzo, V. M., and Cayer, D.: Plasma Vitamin C levels in Patients with Peptic Ulcer: Response to Oral Load Test of Ascorbic Acid, *Gastroenterology* 8:754-761, 1947.

210. Brown, S., and Harper, F. G.: Roentgen Diagnosis of Duodenal Ulcer in the Right Lateral Decubitus Position, *Radiology* 47:575-582, 1946.

211. Kay, A. W.: Effect of Water on Gastric Motility: A Test for Duodenal Ulcer, *Lancet* 1:448-450, 1947.

that patients with peptic ulcer either do not manifest this inhibition or show a reverse response (increased peristalsis). A tambour-kymograph unit, with a modification of Carlson's technic, was used. Thirty normal subjects manifested inhibition of gastric motility as expected. Sixty-eight of 90 patients with symptoms of duodenal ulcer and a roentgenologically demonstrable crater showed increased motility (reversed response), and 22 maintained their gastric contractions. A normal (inhibition) response was observed in 15 patients who had been symptom free for at least a year after perforation of a duodenal ulcer and whose roentgenograms did not demonstrate an active ulcer. A normal response was observed in 33 of 34 patients with gastric lesions (12 with ulcer and 22 with carcinoma). A reversed response was recorded in 1 patient with gastric carcinoma in whom invasion of the duodenum was revealed at laparotomy. Gastric contractions were excited in 2 of 9 patients with acute cholecystitis, and in 1 of these laparotomy revealed empyema of the gallbladder, which was adherent to the duodenum. Carlson's view that the inhibitory effect of cold water on gastric motility is due to afferent stimuli arising in the gastric mucosa should be modified, according to Kay, in favor of the theory that the receptors for their reflex are in the duodenum.

According to Gershon-Cohen,<sup>212</sup> the duodenum houses a mechanism influencing gastric tone, peristalsis, pyloric action and secretion. Experiments are cited to demonstrate that intraduodenal instillation of hydrochloric acid, hypertonic alkaline solution, other hypertonic solutions of electrolytes, fats or fatty acids inhibits gastric peristalsis and induces pyloric closure. A critical threshold level of stimulation of the "duodenal mechanism" regulates the peak of acid gastric secretion. Because this threshold level is altered by the inflammatory processes of duodenal ulcer, characteristic disturbances in gastric motor and secretory activities take place. It is concluded that persistent disturbances in the duodenal mechanism should arouse suspicion that a duodenal ulcer is not healed although symptoms may have disappeared and the roentgenograms may be normal.

Although these observations are of physiologic interest, it is the opinion of the reviewers that the procedures outlined are not practicable in the diagnosis of an active duodenal ulcer and are distinctly inferior to careful analysis of the symptoms and competent roentgen examination.

*Differences Between Gastric and Duodenal Ulcer.*—Hollander<sup>213</sup> discusses some of the clinical and physiologic differences between gastric and duodenal ulceration. He believes that Shay's theory accounts satis-

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212. Gershon-Cohen, J.: A Duodenal Mechanism Regulating the Motor and Secretory Activity of the Stomach, *Radiology* **48**:232-238, 1947.

213. Hollander, F.: Are Gastric Ulcer and Duodenal Ulcer Different Diseases? *S. Clin. North America* **27**:265-271, 1947.



factorily for the dissimilarities in secretory and motor response between patients with duodenal ulcer and those with gastric ulcer, i.e., the possible existence in the normal duodenum of one or two inhibitory mechanisms for the control of motor and secretory acidity of the stomach. Most patients with duodenal ulcer exhibit a considerable disturbance in these inhibitory mechanisms whereas patients with gastric ulcers do not. It is emphasized that the physiologic differences existing between gastric and duodenal ulceration are a consequence of the location of the lesion rather than a cause of it.

*Rate of Healing.*—The time required for the healing of the crater was studied by Cummings, Grossman and Ivy<sup>214</sup> in a series of 69 patients, 63 with duodenal ulcer and 6 with gastric ulcer, receiving milk and cream, a soft diet, an alkaline mixture of sodium bicarbonate and calcium carbonate and small amounts of phenobarbital and belladonna. Healing time was construed as the time interval between the original roentgen visualization of the crater and its subsequent disappearance. When the case in which two hundred and thirty days were required for "healing" is discounted, the average time was thirty-seven days for duodenal ulcer, with a range of thirteen to sixty-eight days, and forty-two days for gastric ulcer, with a range of eighteen to sixty-eight days. No correlation was found between the size of the crater and the rate of healing or between the age of the patient or the duration of symptoms and the time of healing. Pollard and his associates<sup>215</sup> noted considerable variation in the time required for the healing of craters in 100 cases of gastric ulcer.

*Tobacco.*—An investigation by Jamieson and others<sup>216</sup> of the smoking habits of 473 patients who recovered from perforation disclosed no evidence that an increase or a decrease in smoking influenced the severity of the symptoms.

*Diabetes Mellitus and Peptic Ulcer.*—Of 94 patients with both peptic ulcer and diabetes studied by Wood,<sup>217</sup> 59 had had diabetes for varying periods before the onset of ulcer symptoms; the remaining 35 had peptic ulcer first and later diabetes mellitus. The acidity seemed to be somewhat lower than the average for patients with ulcer. The following complications occurred in 62 of the 94 patients: 24 had gross or acute massive hemorrhage, and 8 had persistently positive reactions to tests for

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214. Cummings, G. M., Jr.; Grossman, M. L., and Ivy, A. C.: A Study of the Time of "Healing" of Peptic Ulcer in a Series of Sixty-Nine Cases of Duodenal and Gastric Craters, *Gastroenterology* 7:20-37, 1946.

215. Pollard, H. M.; Bachrach, W. H., and Block, M.: The Rate of Healing of Gastric Ulcers, *Gastroenterology* 8:435-437, 1947.

216. Jamieson, R. A.; Illingworth, C. F. W., and Scott, L. D. W.: Tobacco and Ulcer Dyspepsia, *Brit. M. J.* 2:287-288, 1946.

217. Wood, M. N.: Chronic Peptic Ulcer in Ninety-Four Diabetics, *Am. J. Digest. Dis.* 14:1-11, 1947.

occult blood in the stool. Perforation occurred in 10, and retention was observed in 32, surgical intervention being necessary in 18.75 per cent of these. Advanced arteriosclerosis was present in most of those who had troublesome bleeding.

*Size of Gastric Ulcer.*—In a series of 384 patients with gastric ulcer the lesions measured more than 1.5 cm. in the longitudinal axis in 41 per cent and more than 3 cm. in 6.5 per cent.<sup>218</sup> The relative incidence of larger ulcers increased with age. A high proportion of the larger lesions occurred in the body of the stomach, whereas smaller ulcers were found more often at the pyloric end.

*Postbulbar Ulcer.*—Sixteen cases of duodenal ulcers located beyond the bulb are reviewed;<sup>219</sup> in 75 per cent typical ulcer symptoms were present, and bleeding occurred in 37 per cent. The diagnosis was based on the roentgenologic findings except in 1 case, in which the condition was found surgically.

Kraemer<sup>220</sup> describes a 5 cm. duodenal ulcer located at the ampulla of Vater, with fatal hemorrhage from an erosion into the pancreaticoduodenal artery.

*Hyperparathyroidism and Peptic Ulcer.*—The coexistence of a healed duodenal ulcer, a healed jejunal ulcer and a pronounced clear cell hyperplasia of the parathyroid glands and primary hyperparathyroidism is described.<sup>221</sup> Death resulted from renal insufficiency secondary to nephrocalcinosis. Of interest is the fact that gastrointestinal symptoms presumed during life to be due entirely to the ulcer appeared in retrospect to have been manifestations of severe hyperparathyroidism. Two similar cases had been reported previously. All 3 patients had received large amounts of calcium and phosphorus in the diet. The authors suggest a possible relationship between long term ulcer therapy, with a high intake of milk, and the development of hyperparathyroidism. The reviewers have not encountered a case similar to the one described and consider the possibility most unlikely.

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218. Krisnapoller, N. H.: Röntgenologisches und Klinisches über das grosse Magengeschwür, *Gastroenterologia* **71**:142-170, 1946.

219. Falla Alvarez, L. and Farinnas, P. L.: Postbulbar Duodenal Ulcers, *Gastroenterology* **8**:1-14, 1947.

220. Kraemer, M.: Clinical Pathological Report, *Gastroenterology* **7**:687-691, 1946.

221. Rogers, H. M.; Keating, F. R., Jr.; Morlock, C. G., and Barker, N. W.: Primary Hypertrophy and Hyperplasia of the Parathyroid Glands Associated with Duodenal Ulcer, *Arch. Int. Med.* **79**:307-321 (March) 1947.

*Pituitary Tumor and Peptic Ulcer.*—Two patients with coexistent peptic ulcer and pituitary tumor are reported.<sup>222</sup> An intrasellar tumor was present in 1 patient; the other had acromegaly.

*Medical Treatment.*—The casual reader of therapeutic reports must be impressed by the fact that “good results” are almost always recorded. This is true in regard to the time-honored methods as well as to the newer procedures. Furthermore, the authors usually present a rational basis for the therapy used and one which is valid to them. The skeptic finds it difficult to reconcile the various concepts and is tempted to interpret the outcome as evidence of the natural cyclic course of the disease or as the result of some unsuspected component mutual to the different procedures, such as suggestion and psychotherapy. In the opinion of the reviewers, the alleged “good results” must be critically analyzed, the natural history of the disease and the many facts which are known, as well as those still unknown, being borne in mind.

Gatewood<sup>223</sup> reemphasizes the need for individualization; the aggressive, hard driving businessman who is unsuited by temperament and occupation to a medical regimen may require surgical treatment; the patient in whom flare-ups are associated with emotional storms needs proper psychiatric attention, the person with an excessive night secretion may be best treated by means of vagotomy and patients with lesions not differentiated from carcinoma require gastroscopic study and laparotomy. The fundamental principle of the Sippy treatment is the control of free hydrochloric acid in the stomach throughout the day and night. The diet should be high in protein which has a high acid-combining value. Sodium bicarbonate is not recommended because of its tendency to disturb the acid-base equilibrium. The calcium compounds are advantageous because of their excellent neutralizing ability and of the relative rareness with which they cause untoward effects.

Tanner<sup>224</sup> considers rest in bed the most important factor. Recumbency diminishes gastric activity, decreases venous stasis, increases blood supply and even alters the acidity of the fluid bathing the ulcer on the lesser curvature. Gastrectomy is regarded as the ideal form of surgical treatment. The author attributes failure in 20 of his cases to the fact that despite objective signs of ulcer the ulceration was not the cause of symptoms.

Snorf<sup>225</sup> points out that complications constitute an intimate part of the life cycle of ulcer and influence the therapy.

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222. Wilson, H. T.; Olson, J. D., and Rivers, A. B.: Pituitary Tumors and Peptic Ulcers, *Rev. Gastroenterol.* **13**:371-373, 1946.

223. Gatewood, L. C.: Peptic Ulcer, *M. Clin. North America* **31**:10-112, 1947.

224. Tanner, N. C.: The Management of Peptic Ulcer, *Bristol Med.-Chir. J.* **63**:16-30, 1946.

*Aluminum Hydroxide.*—Thirty-two patients with ulcer were hospitalized and were subjected to a basic hospital regimen in which non-reactive aluminum hydroxide was used; 31 controls were treated similarly except that the reactive aluminum hydroxide was used.<sup>226</sup> The nonreactive form produced no greater clinical improvement than did the reactive form. No constant effect on gastric acidity was observed. The combination of colloidal aluminum hydroxide gel and magnesium hydroxide is regarded by Jankelson as a more effective buffer in the stomach than colloidal aluminum hydroxide gel alone.<sup>227</sup> Concretions of aluminum salts of fatty acids were noted.<sup>228</sup>

*Resins.*—On the basis of studies in rats fed diets containing “amberlite IR-4” for a period of eight months, Segal and his associates<sup>229</sup> conclude that the toxicity of the resin for rats is negligible. When it was given to 30 patients with peptic ulcer<sup>230</sup> all but 1 experienced relief of pain; healing occurred in some. Though the preparation has an unpleasant taste and nausea and vomiting sometimes occurred, no serious toxic effects were noted. Similar results are reported by Kraemer and Lehman.<sup>231</sup> The advantage of this preparation over the effective, inexpensive antacid, calcium carbonate, remains to be established, in the opinion of the reviewers.

*Protein Hydrolysates.*—Protein hydrolysate was given to 134 patients in the amount of 0.6 Gm. per kilogram of body weight.<sup>232</sup> The remainder of the diet was composed of “dextri-maltose” so as to afford 40 to 50 calories per kilogram. The mixture was dissolved in water and divided into eight feedings. After a two week period without pain, food was substituted for one hydrolysate feeding: a normal bland diet was

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225. Snorf, L. L.: The Influence of Complications on the Treatment of Peptic Ulcer, *Am. Pract.* 1:401-408, 1947.

226. Smith, F. H.: Nonreactive Aluminum Hydroxide in the Treatment of Peptic Ulcer, *Gastroenterology* 8:494-503, 1947.

227. Jankelson, I. R.: Colloidal Aluminum Hydroxide Gel and Magnesium Hydroxide in the Management of Peptic Ulcers, *Am. J. Digest. Dis.* 14:11-12, 1947.

228. Child, G. P.; Hall, W. K., and Averbach, S. H.: The Formation of Concretions of Aluminum Salts of Fatty Acids After the Use of Aluminum Hydroxide, *Am. J. Digest. Dis.* 14:63-64, 1947.

229. Segal, H. L.; Hodge, H. C.; Watson, J. S., and Coates, H.: A Polyamine Formaldehyde Resin: III. Chronic Toxicity Experiment in Rats, *Gastroenterology* 8:199-201, 1947.

230. Spears, M. M., and Pfeiffer, M. C. J.: Anion Exchange Resin and Peptic Ulcer Pain, *Gastroenterology* 8:191-198, 1947.

231. Kraemer, M., and Lehman, D. J., Jr.: The Treatment of Peptic Ulcer with Anion Exchange Resins, *Gastroenterology* 8:202-204, 1947.

subsequently resumed gradually. Satisfactory results are reported for 118 patients. Of the 16 who did not improve, 2 had hemorrhage and 2 had perforation.

Thirteen patients with duodenal ulcer, 1 with gastric ulcer and 1 with combined duodenal and gastric ulcer were given 1,500 cc. of a 6 per cent solution of protein hydrolysate daily for an average of nine days.<sup>233</sup> Roentgenograms showed that the ulcer disappeared in 9 cases and was decidedly improved in 5; 1 patient failed to respond. Twenty-six patients with ulcer treated with protein hydrolysate for a two to three week period experienced a satisfactory remission.<sup>234</sup> The frequency of relapses was not diminished, however. Changes in the serum protein and hemoglobin levels were inconsistent. The beneficial effects of protein hydrolysate are ascribed to its buffering action and to the increased nitrogen intake. It should be pointed out that despite various clinical reports on the efficacy of amino acid preparations in the management of peptic ulcer there is no conclusive evidence as yet that a protein deficiency uniformly occurs in the patients or that protein hydrolysates are therapeutically superior to the standard antacid regimen.

*Parenteral Therapy.*—Faroy and his associates<sup>235</sup> obtained satisfactory results in the "control" of acute peptic ulcers after injection of milk proteins intravenously.

Satisfactory results are recorded in the treatment of peptic ulcer by the combined use of "larostidin" (histidine monohydrochloride), an extract of the gastroduodenal mucosa and the program of Meulengracht.<sup>236</sup> The authors add that antispasmodics, sedatives and absorbent powders are important adjuncts in treatment.

Bernstein<sup>237</sup> treated 75 patients with peptic ulcer with an average of twenty daily injections of 0.2 mg. of histamine diphosphate. Fifty pa-

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232. Ruggiero, W. F.; Co Tui, and Bianco, A. A.: The Management of Ambulatory Peptic Ulcer Patients with Protein Hydrolysates, *New York State J. Med.* **46**:2395-2398, 1946. Co. Tui: The Ambulatory Treatment of Peptic Ulcers with Protein Hydrolysates and Dextri-Maltose, *Rev. Gastroenterol.* **14**:108-128, 1947.

233. Kimble, S. T.: A Preliminary Report on Protein Hydrolysate Therapy for Peptic Ulcer, *Gastroenterology* **8**:467-475, 1947.

234. Hodges, H. H.: Protein Hydrolysate Therapy for Peptic Ulcer: Report of Twenty-Six Cases, *Gastroenterology* **8**:476-493, 1947.

235. Faroy, G.; Arnous, J., and Fénéon, J.: Treatment of Gastroduodenal Ulcers with Intravenous Injection of Milk Proteins, *Presse méd.* **55**:313-314, 1947.

236. Pulver, W., and Meier, H.: Vergleichende Beobachtungen Zwischen der Larostidin-, Robuden- und der diätetischen Behandlung der Ulcera ventriculi et duodoni, *Schweiz. med. Wchnschr.* **76**:1151-1153, 1946.

237. Bernstein, B. M.: Histamine in the Treatment of Peptic Ulcer, *Ann. Int. Med.* **26**:852-857, 1947.

tients (66 per cent) were apparently relieved of pain after the fourth injection; 82 per cent were relieved after the tenth injection. Five patients did not respond; in 1 fatal perforation and hemorrhage developed during treatment, and another had a perforation soon after the histamine injections were begun. Twenty-six patients were considered to have been protected against an anticipated recurrence. The reviewers are not impressed by the evidence presented in this and in preceding reports on parenteral therapy. It is pertinent to recall the apparently "beneficial" effects reported after the use of isotonic solution of sodium chloride and of distilled water given parenterally.

*Enterogastrone*.—Greengard and his associates<sup>238</sup> describe a method for the preparation of an enterogastrone concentrate of uniform potency and suitable for parenteral injection in man. Twenty-five Mann-Williamson dogs were treated with 150 mg. of an enterogastrone concentrate daily. Fifteen animals died within the twelve month period of injection, 8 from ulcer and 7 from other causes, and 10 remained free of ulcers during the treatment period. One died of perforation twenty-eight months after treatment, 8 died from miscellaneous causes eleven to forty-eight months after treatment and at autopsy were found to be free of ulcers and 1 is still living five years after treatment. The 10 dogs given control injections of pork muscle extract all died of ulcer in an interval similar to that observed for the untreated Mann-Williamson animals. Eight dogs were treated with the more highly purified concentrate given intramuscularly in one daily 100 mg. dose. Three died within the twelve month period, 1 from ulcer and the other 2 from extraneous causes; of the 5 remaining animals, 3 died from causes other than ulcer fourteen to eighteen months after cessation of therapy; 1 is living and is in excellent condition despite the fact that for three years ulcer therapy was not applied and 1 died of a perforated ulcer after two and a half years. Carefully selected patients with a history of ulcer for five years or more were treated with 200 mg. of enterogastrone. Thirty-two were treated three times a week and 26 six times a week; all were treated for a year except 30. The patients were allowed a modified ulcer diet and antacids for the control of pain; follow-up was made three to four times a year after treatment. The results to date suggest that enterogastrone is effective in preventing recurrences during the treatment period and for an unestimated length of time after discontinuance of the treatment. Pain at the site of the injection was an undesirable but not an intolerable reaction. Vasodepressor reactions were noted in dogs and in 2 patients in

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238. Greengard, H.; Atkinson, A. J.; Grossman, M. I., and Ivy, A. C.: The Effectiveness of Parenterally Administered "Enterogastrone" in the Prophylaxis of Recurrences of Experimental and Clinical Peptic Ulcer, *Gastroenterology* 7:625-649, 1946.

whom a gluteal vein was accidentally entered. Urticaria developed in 3 patients sensitive to pork. The mechanism of the protection is not known, but apparently it is not due to an inhibition of gastric secretion. Hubacher<sup>239</sup> reports beneficial results from the use of Swiss-made gastric and intestinal extracts in 44 of 54 cases. Follow-up studies extended over sixteen months. A rapid decrease in the size of the crater was noted in the patients favorably affected. Patients were given twelve to twenty-one injections either daily or three times a week. At the same time tablets containing the water-insoluble portions of the extracts were given orally. Gastric acidity values before and after therapy are not recorded. Surkes<sup>240</sup> reviews observations on 92 patients with gastroduodenal ulcer treated with extracts from the gastrointestinal mucosa. The preparations were administered both by intragluteal injection and orally. "Favorable results" are reported for 82 per cent of the patients with gastric ulcer and for 92 per cent of the patients with duodenal ulcer.

It is clear that the use of enterogastrone and other extracts in the treatment of peptic ulcer is still distinctly in the experimental stage, with little likelihood of their proving of great value therapeutically unless much more potent and at the same time less irritating preparations can be obtained.

*Massive Hemorrhage.*—Jones<sup>241</sup> discusses in detail the various causes of bleeding from the gastrointestinal tract and their management; this article can be read with profit for its comprehensive and logical approach.

Among 140 patients with hemorrhage reviewed by Wilkinson and Tracey,<sup>242</sup> gross hemorrhage constituted the first symptom of ulcer in 70; only 1 of these died from the original hemorrhage, and 2 died from subsequent hemorrhages. Sixty patients had but one gross hemorrhage; 78 per cent of these responded well to medical treatment. Seventy-four had had more than one hemorrhage before their admission to the hospital; of these, only 25 per cent responded to medical management and had no recurrent hemorrhages. Sixty-one per cent were subjected to operation; hemorrhage recurred after surgical intervention in one third of this group. Forty-one patients of the entire series underwent subtotal gastrectomy; hemorrhage recurred after surgery in 24 per cent of this group.

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239. Hubacher, O.: Peptic Ulcer with Gastric and Intestinal Extracts, *Lancet* 2:272-274, 1946.

240. Surkes, A. W.: Internal Treatment of Gastric and Duodenal Ulcer, *Schweiz. med. Wchnschr.* 77:455-458, 1947.

241. Jones, C. M.: Diagnostic and Therapeutic Considerations of Gastrointestinal Bleeding, *New England J. Med.* 235:773-776, 1946.

242. Wilkinson, S. A., and Tracey, M. L.: The History of Hemorrhage in Peptic Ulcer, *Gastroenterology* 7:450-455, 1946.

One hundred and twenty-four patients were treated medically, with recurrent bleeding in 30 per cent. Of 16 patients operated on without previous medical treatment, 25 per cent suffered subsequent hemorrhage. Wilkinson and Tracey suggest that although recurrent hemorrhages will develop in about 25 per cent of patients regardless of the type of treatment medical management will prevent recurrence of bleeding in many patients with a history of but one previous episode. However, if multiple hemorrhages have occurred, subtotal gastrectomy is the procedure of choice. This analysis indicates that the first hemorrhage is not so likely to be fatal as are subsequent ones, that patients with multiple hemorrhages do not respond well to medical management and that even radical operations are far from satisfactory in preventing recurrent hemorrhage.

Of 295 patients with gastrointestinal bleeding treated at Los Angeles County General Hospital during the year 1944, 142 had peptic ulcer.<sup>243</sup> Hematemesis was the presenting symptom in 111 of these, and melena was the presenting symptom in the other 31. A clinical diagnosis of esophageal varices was made in 85 of the 153 cases of hematemesis from causes other than ulcer; the mortality was 58.8 per cent. In the remaining 68 cases the bleeding was variously attributed to gastric carcinoma, gastritis, lesions of the small bowel, poisons, metabolic disturbances and unknown causes (6 cases). Schatzki<sup>244</sup> advocates early roentgen examination of patients with gastrointestinal bleeding because of the obvious advantage of an early precise diagnosis of the cause and location of the bleeding. The examination is made without abdominal palpation and with the patient in the horizontal position, peristalsis and gravity (turning the patient from side to side) being used as the means of distributing the barium over the surface of the esophagus, stomach and duodenum.

Roentgen studies of 18 patients three months after their recovery from acute hematemesis revealed a chronic duodenal ulcer in 5, gastric ulcer in 1 and an anastomotic ulcer in 1.<sup>245</sup> Two patients gave a history suggestive of ulcer; no roentgen evidence of ulceration was obtained, and the correct diagnoses for 1 proved to be cirrhosis of the liver and for the other hypertension with severe epistaxis. Six patients gave no history of digestive disturbances, and in the absence of positive findings the hemorrhage was attributed to acute gastric erosions. In one report<sup>246</sup> massive hemorrhage is attributed to ulceration of the mucosa overlying aberrant pancreatic tissue.

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243. Thompson, H. L.; Oyster, J. M.; Heid, J. B., and Morgan, F. M.: Hematemesis; A Study of Underlying Causes, *Gastroenterology* 7:320-331, 1946.

244. Schatzki, R.: Roentgenologic Examination in Patients with Bleeding from the Gastro-Intestinal Tract, *New England J. Med.* 235:783-786, 1947.

245. Cluer, E. H.: Evidence of Ulcer in Hematemesis, *Brit. M. J.* 2:651, 1946.

246. Chapman, B. M.; Vogel, W. F., and Schomaker, T. P.: Massive Gastric Hemorrhage Associated with Aberrant Pancreas in the Stomach, *Gastroenterology* 8:367-374, 1947.



Massive gastrointestinal bleeding arose in 4 children from a Meckel diverticulum, duplication of the terminal ileum, a polyp of the descending colon and a bleeding duodenal ulcer respectively; the ulcer occurred in a 12 year old boy.<sup>247</sup> Schrumph<sup>248</sup> discusses the mechanisms of early and late azotemia.

Among 337 patients hospitalized because of massive hemorrhage from peptic ulcer the mortality rate was 10 per cent for patients operated on early (within forty-eight hours of onset) and 70 per cent for those operated on late (more than forty-eight hours after onset).<sup>249</sup> Large amounts of blood administered as transfusions before, during or after operation were of great value in operations performed for the control of hemorrhage. In the differentiation of fatal and nonfatal types of hemorrhage, the most consistent criteria were failure to improve promptly under a strict regimen of rest in bed, moderate doses of morphine, the withholding of fluids and food by mouth and adequate blood transfusions and the recurrence of hemorrhage.

In a series of 539 patients with hemorrhage due to ulcer treated from 1929 to 1945 the operative mortality decreased from 45 per cent before 1939 to 7 per cent after 1939 and the mortality rate among patients treated medically diminished from 6 to 5 per cent; this was a total decrease in mortality from 9.1 to 5.1 per cent.<sup>250</sup> The improved results are attributed to a better understanding of the nutritional requirements and to the more effective control of shock. Zinninger<sup>251</sup> recommends that patients with known gastric or duodenal ulcer who bleed seriously while under treatment be operated on promptly, either during or immediately after hemorrhage. Patients with a gastrojejunal ulcer who continue to bleed may require surgical treatment. Operation is indicated also for persons with perforation or obstruction in addition to bleeding and for those with repeated severe hemorrhages. The type of operation varies with the individual case, but partial gastrectomy is the procedure of choice whenever possible. Ligation of the vessels around the ulcer may be desirable.

*Pyloric Obstruction.*—Sixty of 72 patients (83 per cent) with pyloric obstruction secondary to peptic ulcer were treated successfully by a conservative regimen comprising gastric lavage with sodium bicarbonate, a

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247. Donovan, E. J.: Gross Intestinal Hemorrhage in Infants and Children, S. Clin. North America **27**:443-446, 1947.

248. Schrumph, A.: Azotemia in Gastro-Intestinal Hemorrhage, Am. J. Digest. Dis. **14**:169-170, 1947.

249. Heuer, G. J.: The Surgical Aspects of Hemorrhage from Peptic Ulcer, New England J. Med. **235**:777-783, 1946.

250. Bohmanson, G.: Surgical Arrest of Massive Hemorrhage, Acta chir. Scandinav. **94**:362-378, 1946.

251. Zinninger, M. M.: The Surgical Treatment of Bleeding Peptic Ulcer, S. Clin. North America **26**:1140-1151, 1946.

six meal diet, antispasmodics and an aluminum hydroxide preparation. Surgical intervention is indicated if there is no improvement after a period of ten days.<sup>252</sup>

*Acute Perforation.*—Crohn, Rouse and Smith<sup>253</sup> discuss the various legal aspects of the relationship between trauma and perforation.

Of 166 patients with acute perforation, 95.8 per cent were males.<sup>254</sup> The chief physical findings were abdominal tenderness (97 per cent), abdominal rigidity (95 per cent), absent peristaltic sounds (73 per cent), subnormal body temperature (68 per cent) and diminished hepatic dullness (65 per cent). The onset of epigastric pain was sudden in 97 per cent of the cases, and bleeding occurred in 13 per cent. A definite or suggestive history of peptic ulcer was obtained in 73 per cent. For the 138 patients treated surgically the mortality was 21 per cent; for the 28 treated medically the mortality was 41 per cent. The diagnosis was established in 11 cases at autopsy. The high mortality rate is attributed to (a) poor nutrition and poor general condition of the charity patients and (b) the variety of operators of varying skill as well as to poor post-operative treatment in some cases. It is recommended that the general condition of the patient be improved by suction, transfusions and infusions of plasma and fluid before operation, even if surgical intervention is delayed a few hours.

Of 20 men with perforation of a peptic ulcer in the service who were observed for a sufficiently long period, 12 were returned to full duty and 3 to limited duty, without subsequent disability for periods ranging from seven months to two and a half years.<sup>255</sup> Interestingly, all perforations occurred shortly after the men were inducted into service; in 14 instances they occurred between seven days and two months after induction. Perforation of a duodenal ulcer occurred during roentgen examination, with spreading of barium throughout the abdominal cavity.<sup>256</sup> In an instance of retroperitoneal perforation of an ulcer on the posterior wall of the duodenum roentgen films demonstrated extravasated air along the crus of the left hemidiaphragm, between the peritoneum and the muscle layer of the diaphragm, and air over the superior pole of the left kidney.<sup>257</sup> A

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252. Seeley, S. A.: Medical Management of Pyloric Obstruction Resulting from Peptic Ulcer, *Am. J. Digest. Dis.* **13**:238-243, 1946.

253. Crohn, B. B.; Rouse, O., and Smith, H. W.: The Relationship of Trauma to the Perforation of Peptic Ulcer, *Gastroenterology* **7**:456-463, 1946.

254. Olson, H. B., and Norgore, M.: Perforated Gastroduodenal Ulcers: A Study of One Hundred and Sixty-Six Cases, *Ann. Surg.* **124**:479-491, 1946.

255. Lynns, S. C., and Sinclair, L. G.: Perforated Peptic Ulcers in Naval Personnel, *South. M. J.* **39**:575-580, 1946.

256. Schilling, J. A.: Perforation of a Duodenal Ulcer During Roentgen Examination, *Surgery* **20**:730-745, 1946.

257. Koenig, E. C., and Culver, G. J.: Retroperitoneal Perforation of the Duodenum, *Radiology* **48**:164-167, 1947.

perforated duodenal ulcer in a boy 14½ years old was treated successfully by subtotal resection of the stomach.<sup>258</sup>

Taylor<sup>259</sup> treated a consecutive series of twenty-eight perforations by gastric aspiration instead of operation; the treatment was based on his observation that early perforations seal themselves if the stomach is emptied and kept empty by aspiration and, further, that gastric contents in the peritoneal cavity will be sterilized and absorbed if the leakage is not gross and the contamination not repeated. Twenty-four of the 28 patients recovered. Of the 4 who died, the outcome in 3 was considered as not related to the method of treatment.

Fourteen consecutive patients with acute perforation were treated conservatively by Visick<sup>260</sup> with morphine, intermittent gastric suction and intravenous administration of sulfathiazole and fluid. The temperature returned to normal in six to eight days. Abdominal rigidity gradually lessened, and it disappeared in two to three days. Pain was relieved in one hour, and it did not return except in 2 cases. Eleven patients recovered completely, 2 died, 1 of pneumonia and 1 of subphrenic abscess, and a third recovered eventually after drainage of a subphrenic abscess which had developed. It is concluded that if the perforation is small and spillage negligible, spontaneous closure, with recovery, may well occur. It should be noted also that among patients with acute perforation the surgical mortality is low. Despite these interesting and encouraging results, the reviewers still regard prompt surgical intervention as the treatment of choice, although Graham<sup>261</sup> permits delay for adequate preoperative preparation.

Kingsbury and Schilling,<sup>262</sup> from a study of 224 consecutive cases, report a total mortality of 13.4 per cent, with an operative mortality of 12.6 per cent. Peritonitis was the chief cause of death. There was a mortality of only 5.1 per cent in the group operated on within six hours of the onset of symptoms. Six and two-tenths per cent of the patients gave a history of one or more previous perforations.

Baritell<sup>263</sup> records a mortality of only 1.1 per cent from a series of eighty-eight consecutive operations for perforated gastroduodenal ulcer.

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258. Orlov, M.: Perforated Ulcer in a Child: Report of a Case, *West. J. Surg.* **55**:326-328, 1947.

259. Taylor, H.: Perforated Peptic Ulcer Treated Without Operation, *Lancet* **2**:441-444, 1946.

260. Visick, A. H.: Conservative Treatment of Acute Perforated Peptic Ulcer, *Brit. M. J.* **2**:941-944, 1946.

261. Graham, R. R.: The Treatment of Acute Perforation of Duodenal Ulcer, *Am. J. Surg.* **72**:802-810, 1946.

262. Kingsbury, H. A., and Schilling J. A.: Acute Perforation of Peptic Ulcer: Early and Late Results, *New York State J. Med.* **47**:372-376, 1947.

263. Baritell, A. L.: Perforated Gastroduodenal Ulcer, *Surgery* **21**:24-33, 1947.

On the basis of an analysis of 200 cases, Johansson<sup>264</sup> finds the prognosis between six and twenty-four hours after perforation now relatively good for patients under the age of 40. The outlook is extremely poor in regard to perforations of more than one day's duration even for young patients; it is considerably worse for women than for men.

In a follow-up study<sup>265</sup> of 244 patients treated by simple suture, 65 per cent reported further symptoms; of these, 33 per cent required further surgical intervention.

Werbel and others<sup>266</sup> found that in 41 per cent of patients recovering from the perforation of a nonresected ulcer symptoms requiring hospitalization subsequently developed. A second perforation occurred in 17 per cent, and 30 per cent required additional gastric operations.

The clinical picture in a 53 year old man with a gastrocolic fistula who had undergone repair of a perforation and a gastroenterostomy fifteen years earlier was that of a severe nutritional deficiency.<sup>267</sup>

*Surgical Treatment.*—The literature on gastric surgery for 1945 is reviewed by Marshall and Schmidt.<sup>268</sup> The numerous papers on subtotal gastrectomy reflect the current popularity of this procedure. In general, the mortality rate has decreased, with the result that the indications for operation have been extended; it is considered indicated primarily in cases of gastric ulcer in which the possibility of malignancy cannot be excluded,<sup>269</sup> and in cases of ulcers with cicatricial stenosis, massive hemorrhage and "intractable pain." These symptoms were found by Thompson<sup>270</sup> in 40 of 50 unselected patients subjected to elective operation. Late results of subtotal gastrectomy are difficult to ascertain. Allen and Welch,<sup>271</sup> in a follow-up study of 136 patients who had survived subtotal gastrectomy for duodenal ulcer, found that, with the exclusion of the cases in which Finsterer resections were carried out (failure occurred in

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264. Johansson, O.: 200 Fälle von perforierenden Magen und Duodenalgeschwüren, *Acta chir. Scandinav.* **95**:233-259, 1947.

265. Houston, W.: The Aftermath of Perforated Peptic Ulcer, *Brit. M. J.* **2**:221-223, 1946.

266. Werbel, E. W.; Kozoll, D. D., and Meyer, K. A.: Surgical Sequelae Following Recovery from a Perforated Peptic Ulcer, *S. Clin. North America* **27**:93-108, 1947.

267. Ruffin, J. M., and Margolis, G.: Clinical Pathological Conference, *Gastroenterology* **7**:118, 1946.

268. Marshall, S. H., and Schmidt, I. C.: Gastric Surgery: A Review of Literature for 1945, *Gastroenterology* **8**:160-174, 1947.

269. Hinton, J. W.: Indications for Surgery in the Treatment of Gastric and Duodenal Ulcers, *Bull. New York Acad. Med.* **22**:623-629, 1946.

270. Thompson, H. L., and Prout, H.: Surgical Treatment of Peptic Ulcer, *Arch. Surg.* **54**:390-413 (April) 1947.

271. Allen, A. W., and Welch, C. E.: Subtotal Gastrectomy for Duodenal Ulcer, *Ann. Surg.* **124**:688-707, 1946.

6 of 7), the late effects were excellent in 87 per cent, "improved" in 6 per cent, and definitely poor in 7 per cent. There were three anastomotic ulcers in the last group, one of which developed ten years after resection. Bartels and Dulin,<sup>272</sup> from a study of 221 consecutive cases, report a reduction in the mortality rate from 28 to 8 to 1.6 per cent, accompanied with a reduction in the rate of recurrence from 14.7 to 1.89 per cent. Miller and Nicholson report similar observations.<sup>273</sup>

Watson<sup>274</sup> attributes most of the bad results to inadequate resection and to the use of an excessively long loop, there being evidence that the shorter the loop the greater the safety from ulceration. Steinberg<sup>275</sup> also found that the standard radical proximal short loop, retrocolic terminolateral gastrectomy with a sufficiently wide stoma, gave maximum protection against jejunal ulcers. There have been numerous publications dealing with gastric resection in the Belgian literature.<sup>276</sup>

Palliative gastric resection, introduced by Florcken in 1928, consisting of subtotal resection distal to the ulcer, is, according to Colp and Druckerman,<sup>277</sup> applicable to (1) juxtaesophageal ulcers and peptic ul-

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272. Bartels, R. N., and Dulin, J. W.: Gastric Resection for Peptic Ulcer: A Study of Two Hundred Twenty-One Consecutive Cases, *Surgery* **21**:496-511, 1947.

273. Miller, T. G., and Nicholson, J. T. L.: Results from Subtotal Gastric Resection in Peptic Ulcer, *Am. J. Med.* **1**:476-484, 1946.

274. Watson, A. B.: Partial Gastrectomy for Simple Ulcer: Review of End-Results of One Hundred and Thirty-Two Cases, with Criticism of Polya Operation, *Brit. J. Surg.* **34**:353-366, 1947.

275. Steinberg, M. E.: Treatment of Recurrent Peptic Ulcers Following Gastric Operations, *Northwest Med.* **46**:114-125, 1947; Reoperative Surgery for Recurrent Peptic Ulcerations, *Surg. Gynec. & Obst.* **84**:1029-1037, 1947.

276. Gallart-Mores, F.: Commentaire sur la pathologie du gastrectomisé pour ulcère, d'après notre statistique, *Acta gastro-enterol. belg.* **9**:215-218, 1946. Van Goidsenhauen, F.; Appelmans, R.; Hendriëhx, M.; Joosseens, J.; Vaylssteke, A., and Staessen, A.: Les suites éloignées de la gastrectomie subtotale du point de vue clinique, *ibid.* **9**:254-299, 1946. DeWitte, F.: Les suites précoces et tardives de la gastrectomie du point de vue radiologique, *ibid.* **9**:303-318, 1946. Delayers, L.: Physiopathologie de la gastrectomie subtotale pour ulcère, *ibid.* **9**:318-350, 1946. Goffaerts, A., and others: La gastrectomie du point de vue chirurgica<sup>1</sup>: Resultats de la gastrectomie (deux tiers); dans le traitement de l'ulcère gastroduodenal, *ibid.* **9**:408-430, 1946. Goedsels, L., and Verdoodt, F.: Les suites précoces et tardives de la gastrectomie, *ibid.* **9**:431-440, 1946. Warmoes, F., and Clewaert, R.: Note sur l'intérêt de la gastroscopie dans le diagnostic des troubles après gastrectomie, *ibid.* **9**:440-442, 1946. Froehlich, A., and Saln, J.: Syndrome d'enterite grave après gastrectomie: lambliase akranglo resistente, *ibid.* **9**:442-445, 1946. Godart, J., and Van Leroberghe, L.: Insuffisance hépatique consecutive a la gastrectomie, *ibid.* **9**:453-455, 1946. Massion, J.: Sur les suites de la gastrectomie pour ulcère, *ibid.* **9**:458-459, 1946. Van Hee, J.: Les suites précoces de la gastrectomie, *ibid.* **9**:460, 1946.

277. Colp, R., and Druckerman, L. J.: Palliative Gastrectomy in Selected Cases of Gastric Ulcer, *Ann. Surg.* **124**:675-687, 1946; A Rational Approach to the Surgery of High Gastric Ulcer, *S. Clin. North America* **127**:231-240, 1947.

cers of the esophagus, (2) ulcers high in the lesser curvature and (3) penetrating ulcers on the posterior wall of the cardia in patients whose general physical condition does not warrant removal of the ulcer. Eight patients were subjected to this procedure, with one postoperative death, presumably due to coronary thrombosis. The remaining 7 were observed for periods ranging from twenty-one months to eight years. Absence of free hydrochloric acid was noted in test meals. All gained weight and were free from gastric symptoms. One patient died from uremia twenty-one months after operation; a healed gastric ulcer was demonstrated at autopsy. Roentgen and gastroscopic studies on the remaining 6 patients gave no evidence of the lesion.

Fallis and Warren<sup>278</sup> favor surgical treatment of jejunal ulcers after a trial of intensive medical therapy. Delannay<sup>279</sup> stresses the importance of adequate resection of the stomach and of the removal of the entire duodenal bulb. The reviewers agree on the desirability of a sufficiently wide resection, but they are not convinced on the value of so-called denudation of the mucosa of the antrum and the duodenal bulb. In a case observed recently, after partial gastrectomy and apparently thorough removal of the mucosa of the antrum and the first portion of the duodenum the twelve hour nocturnal gastric secretion measured approximately 2,000 cc., with a free acidity of 100 clinical units!

*Hypoglycemia After Gastric Resection.*—Intense fatigue several hours after eating in patients who have undergone either a total or a partial gastric resection has been attributed by Conn<sup>280</sup> to postprandial hypoglycemia. The reaction to the oral dextrose tolerance test is characterized by a rapid rise of the normal fasting blood sugar content to hyperglycemic levels during the first hour and a precipitous fall to hypoglycemic levels between the second and fourth hours. A high protein, low carbohydrate diet has given excellent results. A similar conclusion is reached by Adlersberg and Hammerschlag,<sup>281</sup> whose patients complained of fulness, nausea, dizziness, palpitation, sweating, headache, fatigue and weakness appearing two to four hours after meals.

Perman<sup>282</sup> recommends disconnection of the gastrojejunal anastomosis and the establishment of an end to end gastroduodenal anastomosis

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278. Fallis, L. S., and Warren, K. W.: Surgical Treatment of Jejunal Ulcer, *Am. J. Surg.* **72**:4-11, 1946.

279. Delannay, E.: Peptic Ulceration After Gastrectomy, *Mém. Acad. de chir.* **72**:386-388, 1946.

280. Conn J. W.: The Diagnosis and Management of Spontaneous Hypoglycemia, *J.A.M.A.* **134**:130-138, (May 10) 1947.

281. Adlersberg, D., and Hammerschlag, E.: Postgastrectomy Syndrome, *Surgery* **21**:720-729, 1947.

282. Perman, E.: The So-Called Dumping Syndrome After Gastrectomy, *Acta med. Scandinav.* (Supp. 196) **128**:361-365, 1947.

for patients with symptoms of the "dumping" syndrome after gastrectomy. This procedure was carried out in 25 cases, with 1 death from peritonitis. Recurrence of an ulcer in the duodenum was observed in 1 case.

*Vagotomy.*—Dragstedt<sup>283</sup> reemphasizes the importance of acid gastric juice in the pathogenesis of peptic ulcer and describes experiments on completely isolated stomachs secreting large amounts of highly acid gastric juice (1 to 2 liters in twenty-four hours). Typical peptic ulcers frequently appear unless the vagus nerves have been divided. It seems likely that the absence of ulcers in the isolated stomachs after vagus section is due to the greatly diminished secretion characteristic of the animals. Thus in 1 animal the secretion fell from an average of 1,100 cc. per twenty-four hours for a two week period, with a free acidity of 116 clinical units, to an average of 410 cc., with a free acidity of 30 units, after vagal section. A second animal secreted an average of 500 to 800 cc., with a free acidity of 33 to 90 units, before vagotomy; this was reduced to 40 to 100 cc., with a free acidity of 0 to 12 units, after the vagal section. These experimental observations are important in view of the evidence that an excessive continuous secretion of gastric juice occurs in most patients with peptic ulcer. The relief of distress from ulcer following vagotomy is attributed chiefly to the striking reduction in acidity, although the reduction in tonus and in motility of the stomach is also important in that it reduces the exposure of the ulcer to peptic digestion and irritation. Complete division of the vagus nerves results in prompt healing of gastric, duodenal and gastrojejunal ulcers. The healing of gastrojejunal ulcers is particularly impressive. A gastroenterostomy in addition to the vagal section was performed in 62 of 122 patients with duodenal ulcer; no recurrent or stomal ulcers developed in this group.

Healing occurred after supradiaphragmatic section of the vagus nerves in all of 10 patients with gastrojejunal ulcer.<sup>284</sup> The relief of distress uniformly obtained by means of vagotomy was not due to anesthesia of the stomach, since reappearance of typical ulcer pain could be immediately induced in sensitive subjects by the postoperative instillation of acid into the stomach. Ruffin and others,<sup>285</sup> on the other hand, failed

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283. Dragstedt, L. R.: Some Physiological Principles in Surgery of the Stomach, *Canad. M. A. J.* **56**:133-137, 1947.

284. Dragstedt, L. R.; Clarke, J. S.; Harper, P. V.; Woodward, E. R., and Tovee, E. B.: Supradiaphragmatic Section of the Vagus Nerves to the Stomach in Gastrojejunal Ulcer, *J. Thoracic Surg.* **61**:226-236, 1947.

285. Ruffin, J. M.; Grimson, J. S., and Smith, R. C.: The Effect of Trans-thoracic Vagotomy upon the Clinical Course of Patients with Peptic Ulcer, *Gastroenterology* **7**:599-606, 1946. Ruffin, J. M., and Smith, R. C.: The Treatment of Peptic Ulcer with Special Reference to Vagotomy, *Am. Pract.* **1**:118-134, 1947.

to produce pain by the introduction of acid into the stomach after transthoracic vagotomy and hence associate the relief from pain with the decreased motility. The reviewers have themselves repeatedly produced pain after transthoracic vagotomy by the injection of acid solutions into stomachs containing sensitive jejunal ulcers; hence, the pain pathways are intact, and the normal stimulus of acid may be adequate to evoke pain. The decreased motility after vagal section doubtless serves to lessen the acid attack, hasten the process of healing and raise the pain threshold more or less rapidly to the point of insensitivity.

Transthoracic vagotomy was followed by healing or quiescence of gastric, duodenal or marginal ulcers in 56 of 57 cases reported by Grimson and others.<sup>286</sup> After vagotomy, 40 patients experienced an uncomfortable fulness of the stomach, and 28 described swelling or distention of the abdomen. Temporary difficulty in swallowing was noted by 21 and colicky abdominal pain by 38. In 31 cases there was an excessive passage of gas through the rectum; temporary diarrhea developed in 20. The average volume of the nocturnal gastric secretion was reduced in 32 cases from 888 to 340 cc. Reduction of the amplitude of gastric contraction, as judged by balloon study, occurred more consistently than reduction of acidity.

The clinical and laboratory data on a group of 40 such patients were studied by Moore and his associates.<sup>287</sup> The clinical results were good, with healing of the ulcer and no recurrences. Transient, undesirable side effects occurred in about 10 per cent. The fasting acidity and motility gradually returned to normal after one year. The secretory response to insulin-induced hypoglycemia remained abolished in most cases, and the clinical well-being of the patients also appeared to outlast the duration of the early changes in secretion and motility. Similar satisfactory results are reported from the treatment of gastrojejunal and duodenal ulcer by supradiaphragmatic vagotomy<sup>288</sup> and also from treatment by the subdiaphragmatic approach.<sup>289</sup>

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286. Grimson, K. S.; Baylin, G. J.; Taylor, H. M.; Hesser, F. H., and Rundles, R. W.: Transthoracic Vagotomy: The Effects in Fifty-Seven Patients with Peptic Ulcer and Clinical Limitations, *J.A.M.A.* **134**:925-932 (July 12) 1947.

287. Moore, F. D.; Chapman, W. P.; Schulz, M. D., and Jones, C. M.: Resection of the Vagus Nerves in Peptic Ulcer, *J.A.M.A.* **133**:741-748 (Marc 15) 1947.

288. Weinstein, V. A., and Colp, R.: Supradiaphragmatic Vagotomy in Gastrojejunal Ulceration Following Subtotal Gastrectomy for Duodenal Ulcer, *S. Clin. North America* **27**:249-253, 1947. Wulff, H.: Supradiafragmal bilateral vagotomi vid ulcus duodeni sine ventriculi, *Nord. med.* **21**:1226-1228, 1947.

289. Crile, G., Jr.: Subdiaphragmatic Vagotomy: Indications and Technic, *Cleveland Clin. Quart.* **14**:65-75, 1947.



The subcutaneous administration of 10 mg. of urethane of B-methyl choline in a patient with considerable gastric retention after vagotomy led to the restoration of gastric peristalsis and motility and relief of the epigastric distress.<sup>290</sup> Subsequently, oral and sublingual administration of the drug had a similar effect. In another vagotomized patient parenteral administration induced sufficient gastric tonus and peristalsis as well as pyloric relaxation. Strong peristaltic waves noted after five to ten minutes lasted for about forty minutes and could be abolished by the parenteral administration of 0.8 mg. of atropine sulfate. The secretion of acid was also increased.

Hollander<sup>291</sup> describes a physiologic test for the presence of uncut vagal fibers based on the fact that hypoglycemia centrally stimulates vagal activity and thereby increases gastric secretion. The test has proved useful, but the reviewers venture to suggest that a negative result may be obtained, at least temporarily, in the presence of an incomplete section of the nerves.

#### DUODENUM

*Anatomic Variations.*—Friedman<sup>292</sup> studied the position of the duodenum in roentgenograms of approximately 450 patients with a normal alimentary tract. The mean location of the highest point of the first portion of the duodenum was opposite the lower part of the second lumbar vertebra; the position varied between the third and twelfth lumbar vertebrae. The variation was found to be due in part to a downward migration with age of the duodenal high point at a statistical rate of almost half a vertebra per decade. The mean position of the lowest point of the third part of the duodenum was opposite the interspace between the third and fourth vertebrae, the position varying between the second and fifth vertebrae. The third part of the duodenum does not migrate downward with age so that there is a constant tendency toward shortening of the vertical diameter of the duodenal curve as age advances. The most fixed point of the duodenum is the duodenojejunal flexure, opposite lumbar  $2\pm 1$  vertebra. It does not migrate with age. In accordance with the state of fulness of the stomach and duodenum, postural changes may induce an excursion of the duodenum of about  $\pm 2$  vertebrae.

Four cases of redundancy of the first part of the duodenum simulating duodenal ulcer or pseudodiverticulum are reported.<sup>293</sup>

290. Machella, T. E.; Hodges, H. H., and Lorber, S. H.: The Restoration of Gastric Motility by Urethane of B-Methyl Choline After Section of the Vagus Nerves for Peptic Ulcer, *Gastroenterology* 8:36-51, 1947.

291. Hollander, F.: The Insulin Test for the Presence of Intact Nerve Fibers After Vagal Operation for Peptic Ulcer, *Gastroenterology* 7:607-614, 1946.

292. Friedman, S. B.: The Position and Mobility of the Duodenum in the Living Subject, *Am. J. Anat.* 79:147-165, 1946.

293. Slater, I. H., and Lautkin, A.: Redundant Duodenum, *U. S. Nav. M. Bull.* 46:1651-1657, 1946.

*Experimental Duodenal Pouch.*—Sonnenschein, Grossman and Ivy<sup>294</sup> describe a method for the production of a chronic, denervated duodenal pouch in the dog. The transplanted duodenal pouch responds to the ingestion of a meal by an increased rate of secretion lasting several hours. The pouch responds to the intravenous injection of a relatively crude intestinal mucosal extract containing secretin but much less to the injection of pure secretin. It is concluded that the secretion of the duodenum is probably in greatest part produced by Brunner's glands and that the volume of the secretion is regulated by a humoral mechanism. This hormone is to be found in a crude secretin product, but it is not secretin.

*Septum.*—A congenital septum located in the third portion of the duodenum produced an enormously dilated duodenum and obstructive symptoms, which were relieved by duodenojejunostomy.<sup>295</sup>

*Aberrant Pancreas.*—Aberrant normal pancreatic tissue was found at autopsy in the wall of the duodenum in a patient who was the victim of an accidental death.<sup>296</sup> Three similar lesions had been reported previously by Whipple in a series of two hundred and fifty-seven duodenal lesions other than ulcer.

*Diverticula.*—Obstructive jaundice resulted from inflammation of a primary diverticulum located at the ampulla of Vater, with secondary inflammation of the biliary tract.<sup>297</sup> An instance of benign ulceration within a diverticulum of the fourth portion of the duodenum is described;<sup>298</sup> the symptoms were controlled by a strict ulcer regimen, and subsequent roentgen examination demonstrated healing of the crater.

*Ulcer of the Fourth Portion.*—An ulcer of the fourth portion of the duodenum was demonstrated at operation on a 61 year old housewife, who had episodes of epigastric pain and hematemesis for six years.<sup>299</sup> The free acidity after an alcohol test meal was 121 clinical units.

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*Injuries.*—In an analysis of 118 cases of duodenal injuries sustained in World War II, Cave<sup>300</sup> reports a mortality during the first ten days of 55.9 per cent (the mortality in the 10 cases reported in World War I was 80 per cent). Seventy-one per cent of the deaths occurred in the first three days; shock and hemorrhage accounted for 39 deaths, pneumonia 9, anuria 8, peritonitis 3, transfusion reaction 2 and pulmonary embolism 1. The cause of death was unrecorded in 4 cases. Multiple complicating injuries were usually present; vascular injuries were common. Transection of the duodenum occurred in 20 patients; complicating fistula developed in 2 known cases and probably in others. Most of the injuries were repaired by end to end anastomosis.

*Cysts.*—A congenital enterogenous cyst of the duodenum in a 12 year old boy was removed surgically.<sup>301</sup>

*Malignant Tumors.*—Dixon and others<sup>302</sup> report a series of forty-nine neoplasms of the duodenum, exclusive of lesions of the ampulla of Vater. Obstructive features were present in 38 cases, while in 6 anemia resulting from loss of blood was the chief finding. The operative mortality was 22 per cent for the 45 patients subjected to operation. A primary carcinoma of the duodenum is recorded by Rossi.<sup>303</sup>

(To be concluded)

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# Book Review

**Practical Emulsions, Including a Symposium on Emulsifying Agents and Emulsions in Industry.** By H. Bennett, M.D. Second edition. Price, \$8.50. Pp. 568. Brooklyn: The Chemical Publishing Company, Inc., 1947.

This book is chiefly concerned with emulsion technology as applied in industry. It is divided into three parts, comprising several chapters each.

In part I a brief nontechnical discussion is given of the theory of emulsion formation, emulsifying agents, stability of emulsions, dispersing agents and wetting agents, concluding with an extensive list (963) of commercial surface-active agents and their chemical nature which in many instances includes a patent number. A list of demulsifying and defoaming agents is also given.

Part II is a symposium by several authors on specific emulsifying agents. Several of these might be of interest to the physician because of their use in food or medicinal preparations. These include the use of lecithin in the preparation of margarine, doughs from certain types of flour, cosmetic creams, chocolate preparations, etc. The section on surface-active agents as germicides includes a description of such compounds as "zephiran chloride," "phemerol," "ccepryn" and "emulsion 607." These act at high dilutions on specific micro-organisms, have a relatively low toxicity index and have been extensively applied in gynecology, ophthalmology, dermatology and dentistry.

Part III contains formulas in which emulsifying agents are used. These apply to such materials as food emulsions, medicinal preparations, cosmetics and drugs, paints, polishes, textile emulsions, sizings, rot-proof and water-proof materials, cleaners' soaps, antiknock fuels, solidified gasoline and agricultural sprays.

From the foregoing, it is apparent that while this book is unique as a source of practical information on surface-active compounds its interest to the physician is limited to those sections concerned with foods, cosmetics and germicides.

**Nogle respirationsfysiologiske undersøgelser ved lungetuberkulose: Thoracoplastikkens indflydelse paa lungevolumen den alveolaere ventilation belyst ved fractioneret alveoleluftanalyse.** By Ulf Gad. Pp. 159. Copenhagen: G. E. C. Gads Forlag, 1941.

This monograph, written in Danish with an English summary, presents studies in preoperative and postoperative lung volumes and composition of alveolar air on patients with pulmonary tuberculosis subjected to thoracoplasty. The first of three chapters deals with the effect of thoracoplasty on lung volume in 51 subjects. Vital capacity was determined spirometrically and compared with results derived from West's formula. Residual air was determined by the hydrogen dilution method. Patients with tuberculosis usually had lowered total capacities and often relatively high residual fractions preoperatively. Postoperatively, the vital capacity was further reduced, but in 24 per cent the residual air was increased. He found patients to be dyspneic on exertion if vital capacity was less than half of the calculated normal amount. Incidentally, the use of roentgenologic planimetry in estimation of lung volume was found unreliable because of wide individual variation.

The second chapter gives the extremely variable results of testing 78 patients for "mixing capacity" after the manner of Lundsgaard and Schierbeck.

The last chapter reports fractional gas analyses on expired and alveolar air both preoperatively and postoperatively with the use of Sonne and Nielsen's apparatus after single inspirations of pure hydrogen. Hydrogen content on expiration decreased more rapidly than normally, and the rate of decrease varied with the severity of the pulmonary tuberculosis. On the other hand, since oxygen values in expired air were more nearly normal in these subjects, the author assumes that blood flow must have decreased in the poorly ventilated parts of the lungs (62 patients).

The author concludes that dyspnea in his patients was due to changed lung volumes and to disturbed alveolar ventilation and that dyspnea might have been worse but for compensating alterations in alveolar blood perfusion. Ingenious charts are included.

Since this work was published, direct measurements of ventilation capacity have shown that vital capacity taken alone can be no criterion of ventilation. Gray, Cournand and others have further clarified the subject of pulmonary function, developing and applying clinically useful tests in studies made on normal and on diseased subjects.

This study is one of the first to compare strictly preoperative and postoperative testing in large series of cases of thoracic disease requiring surgical treatment; it deserves the attention of those who are interested in respiratory physiology and in thoracic diseases.

**Advances in Internal Medicine.** Edited by W. Dock and I. Snapper. Volume 2. Price, \$9.50. Pp. 642. New York: Interscience Publishers, Inc., 1947.

The second volume of this series contains sections on electrocardiography, circulatory failure, angiocardiology and angiography, surgical treatment of hypertension, surgical treatment of tumors and chronic inflammation of the lung, insecticides, physiologic and medical aspects of aviation and deep-sea diving, penicillin in subacute bacterial endocarditis and other infections, Rhesus antigen, pernicious anemia and other megaloblastic anemias, nutritional requirements in disease and nutritional diseases in the Orient.

The section on electrocardiography is excellent in presentation and illustration. Since there is no other readily available source of all the material presented, this volume becomes more valuable. In the section on circulatory failure the author's concepts are presented. Numerous charts add to the clarity of the presentation. Some of the ideas are controversial.

In the section on angiocardiology the method and clinical applications of contrast visualizations are discussed. The illustrations are well chosen and as a whole are well reproduced. The accompanying diagrams add clarity to the few plates which lack contrast.

The surgical treatment of hypertension is reviewed from the standpoint of anatomy of the sympathetic nervous system, purpose, indications and contraindications and evaluation of results of sympathectomy. The various operative procedures are compared.

The surgical approach to bronchial adenoma, bronchogenic carcinoma, tuberculosis, bronchiectasis and lung abscess is briefly reviewed.

The effectiveness, the methods of application and the toxicity of various insecticides are presented. The greater part of the section is devoted to a discussion of DDT (dichlorodiphenyltrichloroethane).

The two sections on the use of penicillin present concise information on the assay, use, indications, dosage and methods of administration of penicillin. The material presented and an extensive bibliography make these sections extremely valuable.

Although the reviewer would like to have included other "advances" in internal medicine, this volume is recommended.

**Experimental Catatonia: A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology.** By Herman Holland de Jong, M.D. Price, \$4. Pp. 225. Baltimore: Williams & Wilkins Company, 1945.

The experimental production of catatonia in animals by the use of bulbo-capnine was first described by the author and Baruk in 1930. The present book represents an extension and an expansion of that significant research. A variety of substances are now known to produce catatonic signs. The first part of this book consists of detailed and extensive protocols of numerous experimental studies. Catatonia was induced by means of drugs, asphyxiation, centrifugation, surgical occlusion of the carotid arteries, audiogenic stimulation and other methods.

The implications for human pathology, with particular reference to catatonic schizophrenia, are presented in the second part of the book.

Dr. de Jong concludes that experimental catatonia is analogous to epileptiform seizures in that both conditions represent nonlocalized diffuse reactions of the central nervous system. He offers the suggestion that cellular asphyxiation may be responsible for the onset of catatonic signs.

He believes that schizophrenia is primarily an organic disease, the mental symptoms being secondary phenomena. He cautiously suggests that there may be a toxic etiologic agent in this disease since "only alterations of the function of the liver and the intestine proved capable of producing experimental catatonia," lesions of the other organs having no such effect. Abnormal reactions to liver function tests by catatonic schizophrenic patients suggested the possibility of primary hepatic damage resulting in the formation of a toxic protein metabolite which may produce cellular anoxia in the nervous tissues and resultant catatonic signs.

This book is skilfully written and authoritative, and it represents stimulating research by an internationally known scientist. It should be of great interest to physicians and to research workers concerned with the physiologic approach to the baffling problem of the etiology of schizophrenia.

**Hospital Care in the United States.** By the Commission on Hospital Care. Price, \$4.50. Pp. 631. New York: The Commonwealth Fund, 1947.

This royal octavo volume of 630 pages embodies the studies of hospital care in the United States made by the Commission sponsored by the Commonwealth Fund. The obviously correct assumption having been made that hospital care in the United States is inadequate, a huge amount of factual material is assembled in support of this position. Along with this, elaborate recommendations are made, and these are stated in section II in the form of 181 classified propositions. The reviewer is a little uncertain about the categorical way in which some of these propositions are set down. Being himself neither a sociologist nor a statistician but a teacher of medicine, he has scanned closely propositions 50 to 55, which concern medical education. He feels that these propositions at least are somewhat inadequate from the standpoint of the relation of medical education to hospital

service. Indeed, in discussions of this sort it must be clearly realized that the university teaching hospital serves a purpose so entirely different from that of nonteaching hospitals devoted mainly to patient service that the two can hardly be discussed at all under the same heading. It would also have been interesting to have a fuller discussion of the impact of the specialty boards on hospital staffs.

The book is far too comprehensive, however, for a brief review. As a storehouse of factual information it is certainly invaluable, and most of the recommendations are sound and constructive or at least serve as a good starting point for further discussion. This study is beyond question a necessary and outstanding contribution to progress in the field, and its sponsors are to be warmly congratulated.

**Internal Medicine in General Practice.** By Robert P. McCombs, M.D. Second edition. Price, \$8. Pp. 741, with 122 illustrations. Philadelphia: W. B. Saunders Company, 1947.

The first edition of this text was reviewed favorably in the ARCHIVES in 1943. The revised second edition is a satisfactory work which this reviewer would be pleased to use for teaching senior medical students. The arrangement of the material is unusual for the major approach to disease states is through symptomatology rather than through morbid anatomy. The first two chapters, "Fundamentals of Diagnosis" and "Psychiatric Disorders," are well done and serve a useful function in a textbook of general medicine, since attention is directed sharply to the methods and difficulties of diagnosis. Throughout the book the author emphasizes the necessity of early, accurate diagnosis. In addition to the new material on psychiatric disorders, there is a new chapter on vascular disturbances of the extremities. The comments on therapeutic agents and diagnostic procedures have been revised and include appropriate up-to-date material. The style is pleasantly conversational and easy to read. Inevitably, it has been necessary for the author to be dogmatic in the effort to simplify the material, but his views are generally sound and acceptable. The index is adequate, and the illustrations are well chosen and well reproduced. Unfortunately the typography is not always clear due to faulty alinement of letters. This book should be useful to the general practitioner and to others who want a modern, thorough and convenient text on internal medicine.

**Jaundice: Its Pathogenesis and Differential Diagnosis.** By Eli R. Movitt. Price, \$6.50. Pp. 261. London: Oxford University Press, 1947.

The question of what is the trouble with the patient suffering from jaundice is a fairly common one in medical practice. Is the primary lesion in the blood or in the liver or the bile ducts, and if there is obstruction in the bile ducts, is this due to a stone or is it due to a carcinoma around the papilla? Usually an expert in this field of diagnosis can give the answer, and in many cases he can warn the surgeon that he had better not operate since there is little chance of his doing any good and there is a big chance that the shock of the operation will bring the patient's life to a close.

In this book Movitt has gathered together an enormous amount of information relating to jaundice and to what is known today about the diagnosis of the several types of disease. Every internist and gastroenterologist would do well to read this book and to keep it handy near his desk. It begins with chapters on the anatomy and physiology of the liver and the biliary tract and on the metabolism

of the bile pigment. Then follow chapters on the pathogenesis of jaundice, diagnostic procedures and modes of differential diagnosis. Other chapters are on hemolytic jaundice, parenchymatous jaundice\* with acute, subacute and chronic hepatitis and carcinoma involving the liver. The final chapter is on obstructive jaundice.

The book is well and interestingly written and can be heartily recommended.

**Maladies et syndromes rares ou peu connus.** By A. Aimes, M.D. Pp. 208, with 26 illustrations. Paris: Masson & Cie, 1946.

As the title of this monograph indicates, most of the rare medical syndromes are discussed. The syndrome is defined and the characteristics summarized. It is an extremely useful book.

**The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities.**

By Philip Lewin, M.D. Third Edition. Price, \$11 (buckram). Pp. 847, with 389 illustrations. Philadelphia: Lea & Febiger, 1947.

Whether it is logical to assemble in one massive book everything to be known about the foot is an interesting question for discussion. For example, should arthritis of the foot be discussed in a book on arthritis or in a book on the foot? Do the circulatory disturbances in the foot belong under the same covers with bunions or are the latter best dealt with in an orthopedic treatise? Be this as it may, Dr. Lewin's book is now in its third edition, so that there is evidently a place for topographic medicine of this sort. The volume is a handsome one, well and profusely illustrated, and there is a lengthy bibliography. The reviewer is glad to have the book on his shelves.

**Advances in Pediatrics.** Edited by S. Z. Levine, A. M. Butler, L. E. Holt, Jr., and A. A. Weech. Volume 2. Price, \$6.75. Pp. 409. New York: Interscience Publishers, Inc., 1947.

Eleven timely, well written and carefully chosen articles make up the attractive second volume of this book. The contributors, all active workers and acknowledged authorities in selected fields, have condensed and summarized each subject to a remarkable degree. All contributions are organized and set up in a most useful and readable form; the bibliographies are excellent. Helping to bridge the gap which unfortunately must always exist between current publications and textbooks, such a volume will certainly be useful to all workers in this and allied specialties.

**Osteotomy of the Long Bones.** By Henry Milch, M.D. Price, \$6.75. Pp. 294. Springfield, Ill.: Charles C. Thomas, Publisher, 1947.

This interesting book adequately fulfils the author's stated purpose of summarizing the principles of the various types of osteotomy for the general surgeon. The work is not an exhaustive review which might interest particularly the orthopedic surgeon, but the author does bring into the volume a summary of the various types of osteotomy which have gradually been developed for the correction of deformity and the improvement of function.

For the most part, the book provides interesting reading which is easily understood, but included also are several sections of mathematical equations which make



dull reading and are difficult of interpretation by the average reader. It is impossible to express any mathematical formula which will apply in each case, and even if such were possible, the application of an exact formula would be impossible of fulfilment at the operating table.

Aside from the weighty sections on mathematics, the book may be recommended for an over-all picture of the use of osteotomy. The author is to be commended for his study and presentation of a single type of operation which has several varied applications. The book is well planned, the illustrations are exceptionally clear and sufficient reports of cases are given to lend support to the text.

**Kompendium der parasitischen Wurmer in Menschen.** By Hans A. Kreis, M.D. Pp. 133, with 70 illustrations. Basel, Switzerland: Benno Schwabe & Co., 1947. Distributor in United States, Grune & Stratton, Inc., New York.

This little book makes no claim to originality. The author states that there is no similar compendium in the German language, and he has compiled this manual from a variety of sources. Points of note are the excellent illustrations, the key table to the identification of parasites and ova and the good paper and print. The book should have a wide use in countries in which German is spoken.

**Trichomonas Vaginalis and Trichomoniasis.** By Ray E. Trussell, M.D., with an Introduction by E. D. Plass, M.D. Price, \$6. Pp. 288. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

Although the subject of the trichomonas organism would on first thought hardly seem to justify a whole book, it certainly is useful to find between two covers all that is known to date about the biology and the disease-producing capacities of this interesting flagellate. The author has assembled a bibliography of 1,586 titles, and there is a critical discussion of over one hundred agents which have been claimed to be of value in *Trichomonas vaginalis* infections.

**Synopsis of Allergy.** By Harry L. Alexander. Second edition. Price, \$3.50. Pp. 255. St. Louis: The C. V. Mosby Company, 1947.

For a small book, the "Synopsis of Allergy" (second edition) presents an excellent review of present day opinions regarding allergic diseases and the more important causes, diagnostic methods and treatment. It should be a valuable addition to any medical library.

**The Practical Nurse.** By Dorothy Deming, R.N. Price, \$3. Pp. 357. New York: The Commonwealth Fund, 1947.

The Commonwealth Fund has again sponsored a most important book. Recent years have clearly shown that the problems of nursing service cannot be adequately handled by the available supply of trained nurses. Hence, the development of practical nurses to supplement the work done by highly trained experts becomes an obvious need. Mrs. Deming's comprehensive study covers the problem of the practical nurse from every standpoint—historical, educational and economic. It is a book which will be essential to all dealing with problems of nursing service as well as a landmark in the philosophy of nursing education.

## PERIARTERITIS NODOSA

A Case of Fatal Exfoliative Dermatitis Resulting from "Dilantin Sodium" Sensitization

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AND

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CINCINNATI

THE TOXICITY of diphenylhydantoin sodium is well recognized and has been discussed in numerous reports.<sup>1</sup> Cutaneous reactions occur in 5 to 10 per cent of patients receiving therapeutic doses of the drug.<sup>1a b</sup> These reactions may be erythematous, scarlatiniform or morbiliform in character and may be accompanied with conjunctivitis and erosive lesions of the oral mucosa. Withdrawal of the drug usually results in rapid disappearance of the lesions. Exfoliative dermatitis is an occasional serious result of sensitization to diphenylhydantoin sodium ("dilantin sodium"),<sup>2</sup> but only one death clearly attributable to this was discovered in the literature.<sup>3</sup> The pathologic report in this case mentioned numerous hemorrhages in the skin, mouth, gastrointestinal tract and brain, fatty degeneration of the liver and congestion of the spleen.

The present case is of interest in that medication with diphenylhydantoin sodium was continued in the face of a cutaneous reaction and lesions of the mucous membrane. Fatal exfoliative dermatitis resulted, and at autopsy many granulomatous lesions were found in the skin, liver, spleen, kidneys and bone marrow. Many of these lesions were clearly a response to necrosis in the walls of arterioles and presented a clear picture of periarteritis nodosa.

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From the departments of medicine and pathology of Baltimore City Hospitals.

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## REPORT OF A CASE

W. G., a 71 year old Negro, was admitted to Baltimore City Hospital on April 13, 1946, in a stuporous state, with the primary complaint of an ulcerative stomatitis and conjunctivitis which could not be controlled by therapy in the patient's home.

*Past History.*—Except for exanthems in childhood and malaria during adolescence, the patient had always enjoyed good health. During the past two years he became aware of insidiously increasing nocturia, dribbling and incontinence. There was no history of cutaneous disease, hives, asthma or food or drug sensitivity. He had never had any head injuries, coma or convulsions. During the past five years the patient's family physician recorded normal blood pressures, and repeated physical examination had revealed little more than senility and peripheral arteriosclerosis. The prostate was soft and moderately enlarged.

There was no history suggestive of allergy or of epileptic attacks in the patient's family.

In November 1945 the patient had had three generalized convulsions, the first in his life, at about weekly intervals. They lasted several minutes, there was no incontinence or injury and, although the patient was slightly confused, they were not followed by stupor. The patient was treated with diphenylhydantoin sodium, 0.1 Gm. three times daily, by his family physician, with instructions to take the drug only to control convulsions. He had the prescription refilled and took the drug continuously until his admission to the hospital.

During January 1946, loss of appetite and dull pain in the upper abdominal area developed, and on several occasions the patient passed black stools and vomited small amounts of blood. These symptoms cleared when "creamalin" (aluminum hydroxide gel) was administered symptomatically. There was no recurrence.

During the last week of March 1946, he was seen by his physician to have a diffuse maculopapular rash, injection of the scleras and spots on the oral mucosa. This was considered to be measles, as a measles epidemic was present in the community. On April 7 an ulcerative stomatitis developed along the margins of the gums. This spread to the entire mouth and throat in spite of oral penicillin therapy. The patient had been unable to take food or fluids on any of the five days prior to admission.

*Physical Examination.*—The patient was a senile, moderately emaciated, stuporous Negro with considerable dehydration. The temperature, pulse, respiration and blood pressure were within normal limits. The skin was loose and moderately edematous, with pronounced loss of elasticity. Over the entire body small flakes were desquamating, and large sheets were peeling from the palms and soles. There were hard, shotty and discrete nodes in the left cervical area and bilateral inguinal adenopathy. The lids were matted with pus, and the scleras and conjunctivas were injected. There was grade I retinopathy. The nasal mucosa was moderately crusted. The mouth was filled with a thick yellow exudate, which on removal revealed the mucosa to be dehydrated and covered by confluent, indurated, necrotizing ulcers involving the lips, gums, alveolar margins, anterior pillars and palate. The tongue, tonsils and pharynx were not involved. There was notable hyperplasia of the gums around the few carious teeth present.

The chest was of emphysematous contour, with pulmonary fields uniformly hyperresonant to percussion. There was a small area of increased voice sound transmission over the left anterior side of the chest. Throughout the pulmonary fields the breath sounds were harsh and of a bronchial character, with coarse inspiratory

and expiratory rhonchi. The abdomen was normal. Rectal examination revealed a moderately enlarged prostate and large external hemorrhoids. The peripheral arteries were thickened and tortuous. The remainder of the physical examination revealed nothing abnormal.

*Laboratory Data.*—Routine specimens of urine were within normal limits. A moderate hypochromic microcytic anemia was present, with 3,200,000 erythrocytes, 8.5 Gm. of hemoglobin and a hematocrit value of 23.5. The corrected sedimentation rate (Wintrobe) was 12 mm. per hour. The white blood cell count was 6,100 with a normal differential count and no eosinophilia. Examination of the stool revealed no abnormalities. Roentgenologic examination of the lungs and pelvis revealed them to be normal. Other findings were without significance.

*Hospital Course.*—The patient was maintained with small feedings of a high protein and carbohydrate liquid diet, supplemented by parenteral administration of dextrose, "amigen" and vitamins to meet his fluid and caloric requirements. The



Fig. 1.—Photograph of the patient on the fourth day in the hospital.

mouth was irrigated with half strength hydrogen peroxide and the eyes treated with zinc sulfate and epinephrine drops. Penicillin, 40,000 units, was given every three hours.

Biopsy of an inguinal node on the fourth day showed considerable destruction of the normal architecture. The endothelial elements were extremely conspicuous, with capillary proliferation crowding out the lymphoid tissue. The tissue was infiltrated throughout with eosinophils. Pigmented macrophages were present in some areas. This was considered a reactive lymphadenitis secondary to the exfoliative dermatitis.

The patient's general condition remained unchanged. He remained semistuporous and did not gain ground. As the fluid balance became better, the mouth became cleaner, but the ulcers showed no evidence of healing. The skin continued to desquamate in increasingly large sheets (fig. 1). On the fifth

day in the hospital muscular twitchings were noted and the liver was felt several centimeters below the costal margin. On the ninth day the patient quietly died.

*Autopsy.*—An autopsy was performed forty hours after death. Large sheets of desquamating epithelium were present over the entire body. The eyes were matted shut with a purulent exudate. The mucous membrane of the oral cavity were denuded and covered with bloody purulent material. Hard, shotty nodes were felt in the superficial chains.

The bronchi contained a copious yellow purulent exudate, but there was no consolidation of the parenchyma; there was minimal pulmonary edema. The heart weighed 300 Gm. and exhibited moderate arteriosclerotic changes.

The liver was enlarged and weighed 1,350 Gm. The capsule was smooth, but the edges were blunted and the consistency doughy. The lobules were distinct but did not appear engorged. The spleen weighed 110 Gm. The capsule presented a mottled pink and white appearance. On section the parenchyma was firm and the trabeculae prominent.

The renal capsules were stripped with difficulty. The cortex of each kidney was thinned and the surface granular. No petechiae were seen on repeated section. The prostate was diffusely enlarged, and the right lobe contained an encapsulated hard mass. There were enlarged, soft, gray, lymph nodes in the mesenteries, retroperitoneal chains, and in the mediastinum.

The brain was examined in the neuropathology department of the University of Maryland by Dr. John A. Wagner. No gross or microscopic lesions were found other than moderate arteriosclerotic degeneration.

*Microscopic Examination.*—Lungs: The bronchi and the larger bronchioles contained aspirated mucus and an exudate rich in macrophages and eosinophils. Eosinophils constituted about 50 per cent of the leukocytes found in the post-mortem clot in the larger vessels.

Heart: The myocardial fibers were separated by interstitial edema, but no scars or inflammatory lesions were visible in the sections cut.

Liver: There was diffuse cloudy swelling throughout the liver. The portal spaces were infiltrated with mononuclear cells and eosinophils. This infiltration was associated with necrosis of arterioles, and adjacent to the necrotic arterioles there were occasional minute granulomatous foci containing epithelioid cells, macrophages and eosinophils. Some of the parenchyma of the liver proximal to the most markedly involved periportal spaces was likewise necrotic.

Spleen: Many arterioles had partially or completely necrotic walls which were surrounded by eosinophils and mononuclear cells. Among the latter were epithelioid cells arranged in palisade fashion about the affected vessels. There were occasional giant cells. In addition, occasional small vessels contained thrombi, and there were many small foci of necrosis in the pulp. Some of the trabeculae were partially or completely necrotic, and some of these were infiltrated with inflammatory cells or surrounded by epithelioid cells.

Kidneys: Necrotizing inflammatory arterial and arteriolar lesions of the type seen in the liver and spleen were scattered diffusely throughout both kidneys (fig. 2). Some glomeruli were likewise involved in the necrotizing process and were invaded by macrophages and eosinophils. The tubular epithelium showed cloudy swelling, and some of the cells contained hemosiderin granules.

Skin: The sloughing of epidermis was limited to the cornified layer. There were focal accumulations of polymorphonuclear and mononuclear cells deep in the corium, with eosinophils in abundance. In this layer the connective tissue and small vessels were undergoing necrosis.

**Bone Marrow:** The marrow of the sternum and vertebrae was hyperplastic, with a preponderance of nucleated red cells and eosinophils. Few mature cells of the myeloid series were seen. Periarteriolar lesions of the type described previously were observed.

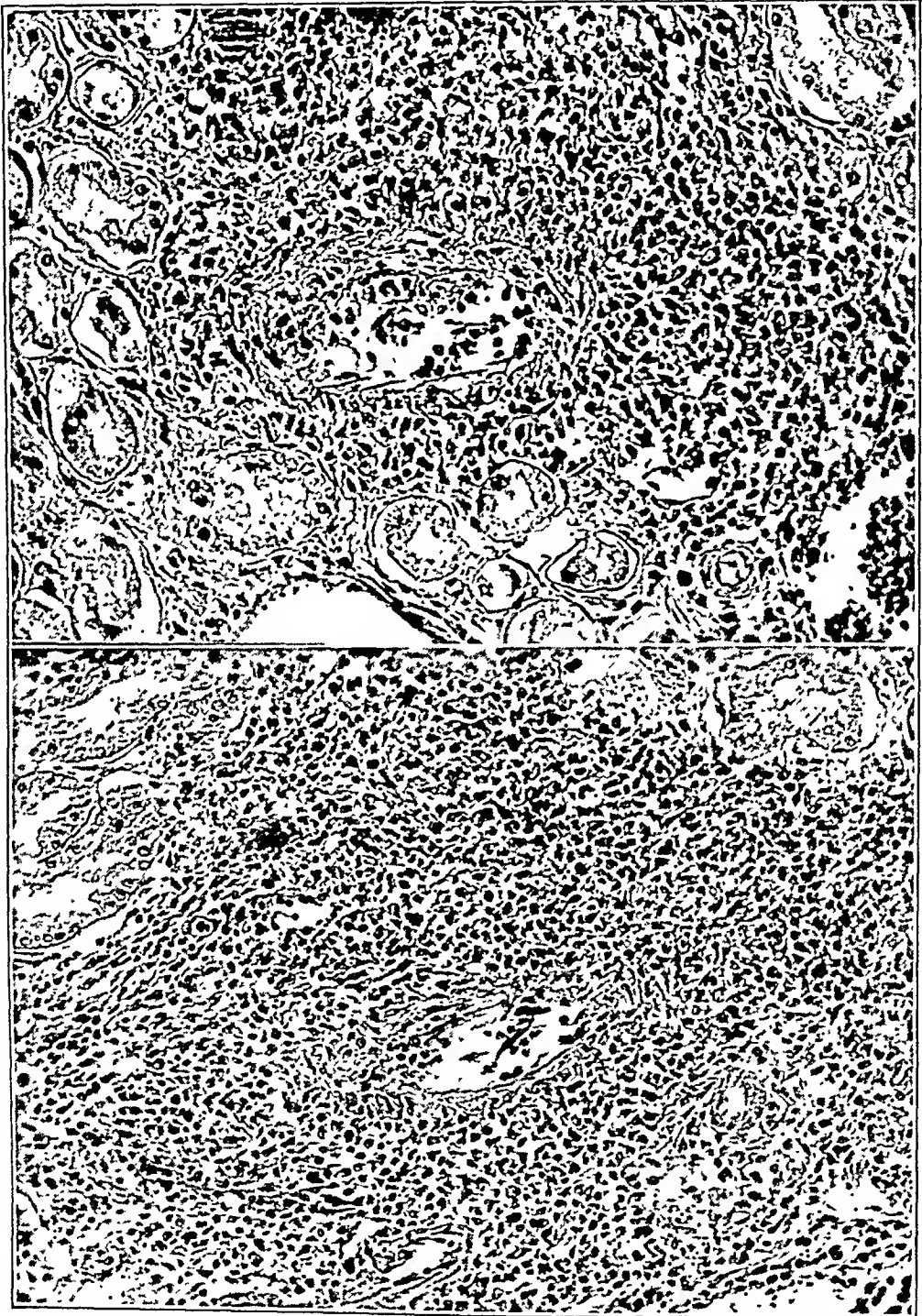


Fig. 2.—Photomicrographs of renal medulla showing necrosis of a small artery and arteriole. The cellular response is composed largely of mononuclear cells and eosinophils. Some of the cells surrounding the larger vessel have an epithelioid appearance and are beginning to orient in palisade fashion.

**Other Organs:** The pancreas, adrenals, stomach and intestine were free from the necrotizing process and exhibited no specific pathologic changes. The prostate was the site of benign hypertrophic changes and chronic inflammation. The lymph nodes did not differ from the one examined at biopsy.

## COMMENT

The clinical reactions resulting from hypersensitivity to diphenylhydantoin sodium are similar to those resulting from sensitization to horse serum, the sulfonamide compounds, barbiturates, "nirvanol" (phenylethylhydantoin) and other drugs. The periarteriolar lesions in the present case are similar to those reported by Rich as occurring in human and experimental serum sickness and in hypersensitive reactions to sulfonamide drugs and to iodine.<sup>4</sup> These lesions are a manifestation of the anaphylactic type of hypersensitivity.<sup>4b</sup>

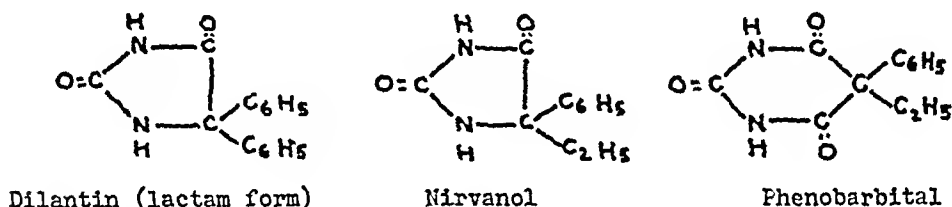


Fig. 3.—Chemical composition of "dilantin" (lactam form), "nirvanol" and phenobarbital.

Ellis has emphasized the chemical kinship existing between dilantin sodium, "nirvanol" and phenobarbital.<sup>5</sup> Thus chemically, "dilantin sodium" is diphenylglycolyl urea, "nirvanol" is phenylethylglycolyl urea and phenobarbital is phenylethyl malonyl urea:

Of this group, "nirvanol" has fallen into disuse because "nirvanol sickness" was an almost constant result. However, as with "dilantin sodium," fatal exanthems were rare, and the vast literature on this drug contains no precise descriptions of the pathologic lesions.<sup>6</sup> Fatal reactions of this type due to the barbiturates, however, have been reviewed in several papers.<sup>7</sup> Although these cases were clinically similar to our case, no mention was made of periarteritis. It therefore remains to be

4. (a) Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *Bull. Johns Hopkins Hosp.* **72**:65, 1943. (b) Rich, A. R.: Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *ibid.* **71**:375, 1942; (c) Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, *ibid.* **77**:43, 1945.

5. Ellis, F. A.: Reactions to Nirvanol, Phenytoin Sodium, and Phenobarbital, *South. M. J.* **36**:575, 1943.

6. Goebel, F.: Fuer und wider die Nirvanolbehandlung der Chorea minor, *Deutsche med. Wchnschr.* **57**:1313, 1931. Madden, J. F.: Nirvanol Eruptions, *Arch. Dermat. & Syph.* **26**:1065 (Dec.) 1932.

7. Wile, U. J., and Benson, J. A.: Exfoliative Dermatitis Due to Phenobarbital with Fatal Outcome: Report of Two Cases, *Ann. Int. Med.* **13**:1243 (Jan.) 1940. Sexton, D. L.; Pike, G. M., and Neilson, A.: Exfoliative Dermatitis and Death Due to Phenobarbital, *J.A.M.A.* **116**:700 (Feb. 22) 1941.

shown whether drugs of this group, other than diphenylhydantoin sodium, are capable of producing periarteritis nodosa.

It is not to be expected that periarteritis nodosa will occur in all patients in whom hypersensitive reactions to a given drug develop. Only some of those in whom serum sickness or cutaneous reactions to the sulfonamide drugs develop become affected with periarteritis nodosa, and the same is true of animals subjected to experimental serum sickness.<sup>4a b</sup> It should be emphasized, however, that the continued administration of a drug after symptoms of hypersensitivity have appeared is fraught with danger.

#### SUMMARY

A case is described of a patient in whom fatal exfoliative dermatitis developed as a result of medication with diphenylhydantoin sodium continued in the face of clear evidences of hypersensitivity to this drug.

At autopsy, inflammatory-necrotizing arterial lesions of the type occurring in serum sickness and in hypersensitive reactions to the sulfonamide drugs and to iodine were present in the liver, spleen, kidneys, bone marrow and skin.

It is reemphasized that continued medication with diphenylhydantoin sodium and certain other drugs after clinical evidences of hypersensitivity have developed may lead to periarteritis nodosa.



# FOOD PROTEIN CONSUMPTION IN GLOMERULONEPHRITIS

Effect on Proteinuria and the Concentration of Serum Protein

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AND

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SAN FRANCISCO

WITHIN the last decade, few studies have been made of the relationship of consumption of food protein to proteinuria and to concentration of serum protein in glomerular nephritis, although previously many such reports appeared in the literature. Additions to the knowledge of renal pathophysiology during this period, however, offer explanations for phenomena previously unexplained, and contradict some interpretations which have been offered in the past. Certain objections now may be made to the technic employed in some of the older investigations. The therapeutic corollary to this relationship still remains a source for controversy, but much evidence has accumulated to show that attempts at treatment with high protein diets in conditions associated with renal damage may not be helpful, as was previously supposed by some, but may be dangerous. For these reasons, the following experiments were undertaken to demonstrate the effect of varying levels of consumption of food protein on proteinuria and the concentration of serum protein in glomerular nephritis.

## METHODS AND REPORTS OF CASES

For this study 2 patients in the degenerative stage of glomerular nephritis were selected. Both were excreting large quantities of protein in their urine, both had low concentrations of serum protein, and both were edematous.

CASE 1.—Mr. A. H., a white carpenter, aged 63, entered the medical ward of Stanford University Hospitals on Oct. 4, 1946, because of dyspnea and massive, generalized edema. For two years prior to admission, he had experienced increasing swelling of his lower extremities, scrotum, hands and face. Gradually in-

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Technical assistance was given by Mrs. Evalyn Barrett and Miss Helen J. Ureen.

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creasing dyspnea and fatigue first appeared eight months before entry. One previous examination of the urine in 1929 was said to have given negative results. No history was obtained of hematuria, other symptoms suggestive of renal disease, cough, orthopnea or pain in the chest.

Physical examination disclosed massive, soft, pitting edema of his lower extremities and scrotum, involving his hands and face to a lesser extent. His fundi showed moderate arteriosclerotic changes, several old retinal scars and a few small hemorrhages. Fluid was present in the right pleural cavity, and a few moist rales were heard at the bases of both lungs. The heart was moderately enlarged, no murmurs were heard, and the rhythm was regular. The blood pressure was 204 systolic and 120 diastolic. Abdominal examination revealed nothing abnormal except edema of the abdominal wall.

Laboratory examination revealed: red blood cells 4,590,000 per cubic millimeter, hemoglobin 70 per cent (Sahli), white blood cells 8,960 and a normal differential count, serum protein 4.62 Gm. per hundred cubic centimeters, serum creatinine 2.07 mg. and serum cholesterol 243 mg. The specific gravity of the urine was 1.015, the  $p_{H6}$ , protein 27.4 Gm. per twenty-four hours, fatty casts 5,000,000 per twenty-four hours, granular casts 1,000,000 per twenty-four hours, red blood cells 14,000,000 per twenty-four hours, white blood cells and epithelial cells 10,000,000 per twenty-four hours and many oval fat bodies. The phenolsulfonphthalein excretion was 18 per cent in two hours, venous pressure 10 cm. of water, circulation time (arm to tongue) 17 seconds and vital capacity 1.9 liters.

CASE 2.—Mr. E. H., a white radio technician, aged 25, entered the medical ward of Stanford University Hospitals on Nov. 1, 1946, because of generalized edema. He had experienced no serious illnesses until 1941, when a severe sore throat associated with fever and cervical lymphadenopathy developed. After physical and laboratory examination in April, 1944, he was accepted for military service. On Oct. 1, 1944, he first noted swelling of his ankles, which rapidly progressed, so that he gained 25 pounds (11.3 Kg.) in one month. From then until entry generalized edema persisted, necessitating fourteen admissions to the hospital for relief of the anasarca with Southey tubes and other measures.

Physical examination showed a marked, generalized, soft, pitting edema of his face, hands, abdominal wall, sacrum and lower extremities. His fundi were normal. Fluid was present in both pleural cavities, but no rales were heard. His heart was not enlarged, there were no murmurs, and the rhythm was regular. His blood pressure was 144 systolic and 90 diastolic. His abdomen contained a moderate amount of fluid.

Laboratory examination revealed: red blood cells 3,450,000 per cubic millimeter, hemoglobin 68 per cent (Sahli), white blood cells 11,800, a normal differential count, serum urea 111.8 mg. per hundred cubic centimeters, serum creatinine 6.85 mg., serum protein 4.59 Gm. and serum cholesterol 547 mg. The specific gravity of the urine was 1.014, the  $p_{H6}$ , protein 13.5 Gm. per twenty-four hours, granular casts 700,000 per twenty-four hours, hyaline casts 300,000 per twenty-four hours, no renal failure casts, red blood cells 12,000,000 per twenty-four hours, white blood cells and epithelial cells 32,000,000 per twenty-four hours and many oval fat bodies.

Case 1 was studied for four consecutive weeks and case 2 for three consecutive weeks. No fever or other complication arose in either patient during the experimental period. The patients were allowed to eat without restriction during the weekends. Biochemical measurements

were made from Monday to Saturday of each week, during which time the patients received diets containing adequate calories and vitamins and a carefully calculated amount of protein. The protein content of the diets was varied at weekly intervals, and ranged from 0.2 Gm. to 2.5 Gm. of protein per kilogram of body weight. The diet containing 2.5 Gm. of protein per kilogram of body weight was not given to the second patient, as it was considered to be too risky in view of his retention of nitrogen. Specific food proteins were not studied.

The schedule for collection of blood and urine was identical during each week. Twenty-four hour urine collections were made from Monday to Wednesday. On Thursdays and Fridays, urine was collected as follows: 7 a.m.—12 noon, 12 noon—5 p.m., 5 p.m.—10 p.m., 10 p.m.—

*Effect of Food Protein Consumption on Serum Concentrations of Urea and Creatinine*

Food Protein Consumption Gm./Kg. Body Wt./Day.	Case No. 1		Case No. 2	
	Serum Urea Mg./100 Cc.	Serum Creatinine Mg./100 Cc.	Serum Urea Mg./100 Cc.	Serum Creatinine Mg./100 Cc.
0.5	31.4	2.05	119.3	7.13
1.5	72.6	2.41	143.2	7.30
2.5	114.0	2.79	.....	....
0.2	45.5	2.42	122.9	7.22

7 a.m. Blood samples were taken at the end of each urine collection period on Thursdays and Fridays, and on Saturday mornings.

Serum protein was determined by the copper sulfate method of Phillips and others,<sup>1</sup> this being checked frequently by a modification of the biuret method of Kingsley.<sup>2</sup> The urinary protein was measured by the biuret method.

## RESULTS

The effects of consumption of different amounts of food protein on proteinuria and on the serum protein concentration are presented graphically in chart 1 for the patient in case 1 and in chart 2 for the patient in case 2.

1. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R.: Copper Sulphate Method for Measuring Specific Gravities of Whole Blood and Plasma, New York, The Josiah Macy, Jr., Foundation, February 1945.

2. Kingsley, G.: The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction, J. Biol. Chem. **131**:197-200 (Nov.) 1939.

*Proteinuria.*—In both cases alterations in the amount of food protein consumed were followed by parallel changes in the quantity of protein excreted in the urine. When the dietary protein was increased, the proteinuria was augmented. Similarly, decreasing the amount of dietary protein resulted in a diminished proteinuria. While these changes in excretion of protein were apparent on the first day of each new level

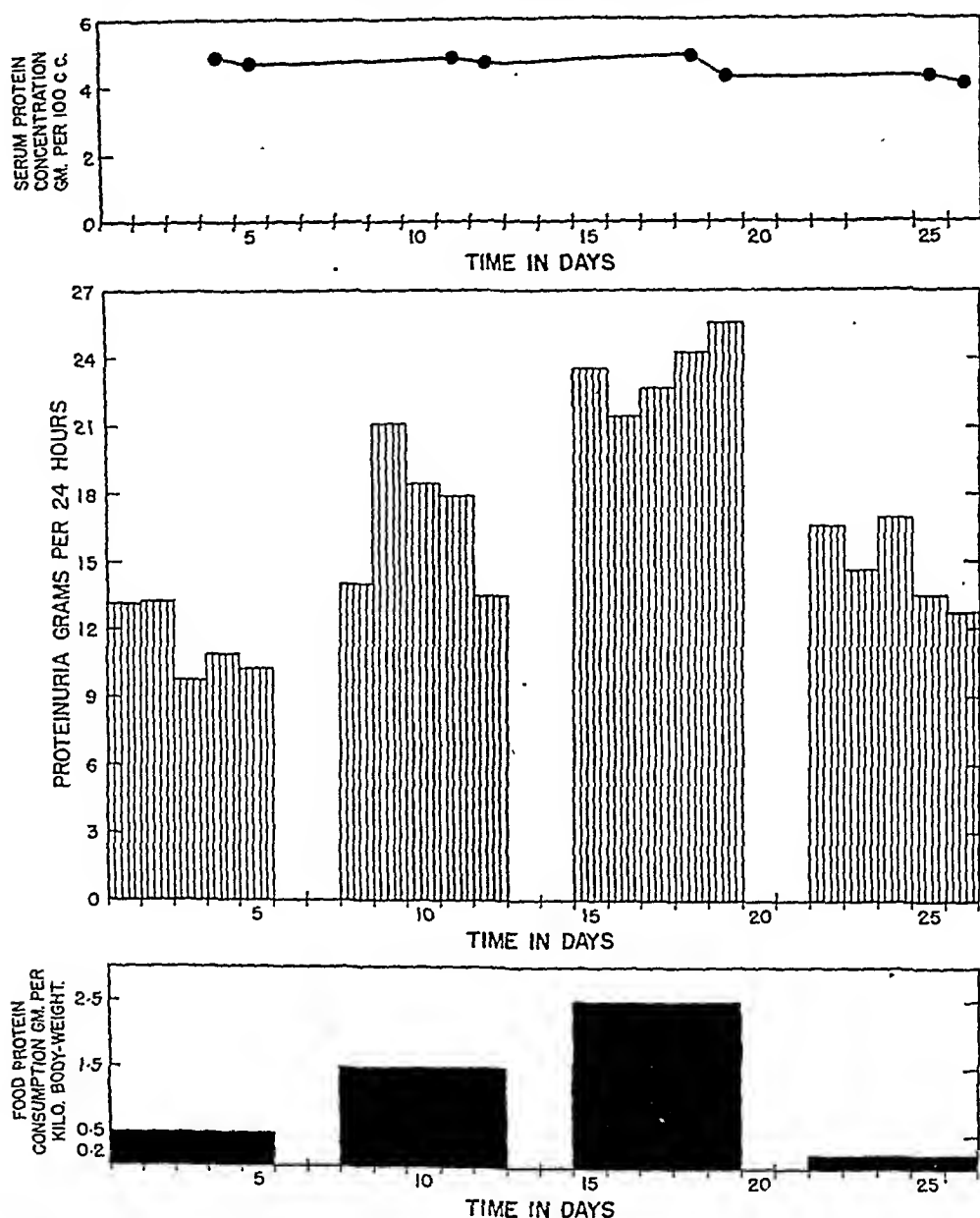


Chart 1 (case 1).—Effect of consumption of food protein on proteinuria and concentration of serum protein.

of food protein consumption, they were not maximum until the new diet had been given for several days. This lag effect is particularly well illustrated in chart 2, when the dietary protein was changed from 1.5 Gm. to 0.2 Gm. per kilogram of body weight.

*Diurnal Variations in Proteinuria.*—The diurnal variations in proteinuria are shown in chart 3 for patient 1 and in chart 4 for patient 2.

In both cases more protein was excreted during the day than at night, the greatest proteinuria occurring during the morning and early afternoon. This variation was independent of the food protein consumed, as similar changes occurred at each level of protein intake.

*Concentration of Serum Protein.*—The concentration of serum protein was unaltered while the patients received nutritionally adequate amounts of dietary protein. Raising the protein intake above 0.5 Gm. of protein per kilogram of body weight did not increase the concentra-

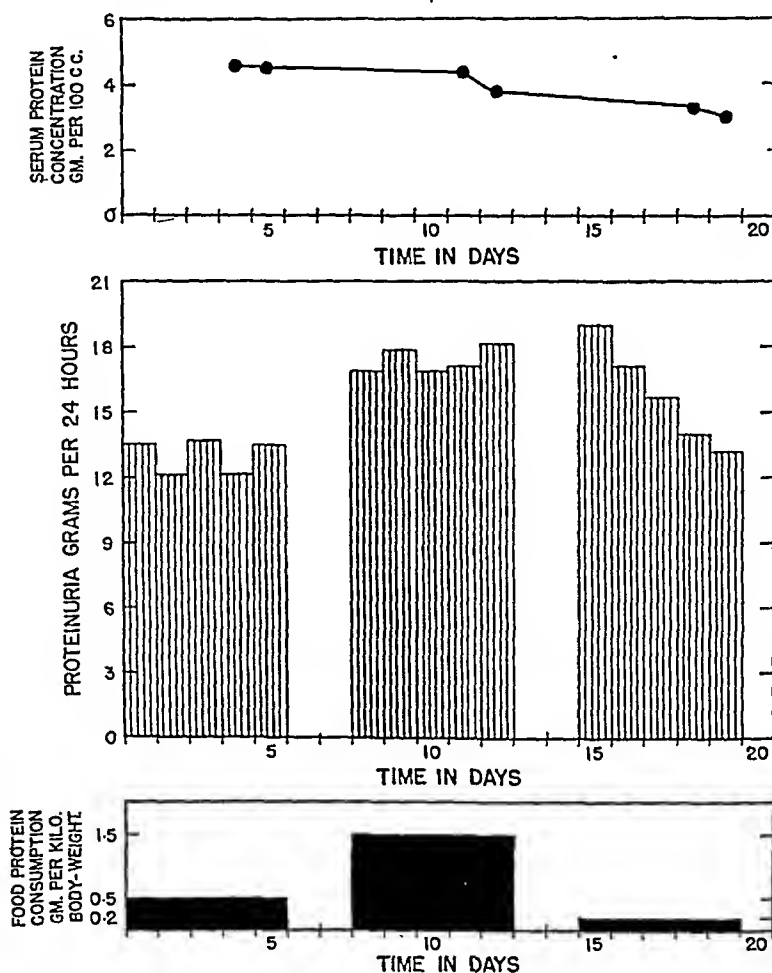


Chart 2 (case 2).—Effect of consumption of food protein on proteinuria and concentration of serum protein.

tion of serum protein. During the week when the food protein consumed by patient 2 was reduced to 0.2 Gm. per kilogram of body weight, an inadequate amount, the concentration of serum protein diminished.

#### COMMENT

Berglund and associates and others described a parallel relationship between the amount of protein consumed and the amount of protein excreted in the urine.<sup>3</sup> All patients except 1 reported on by these in-

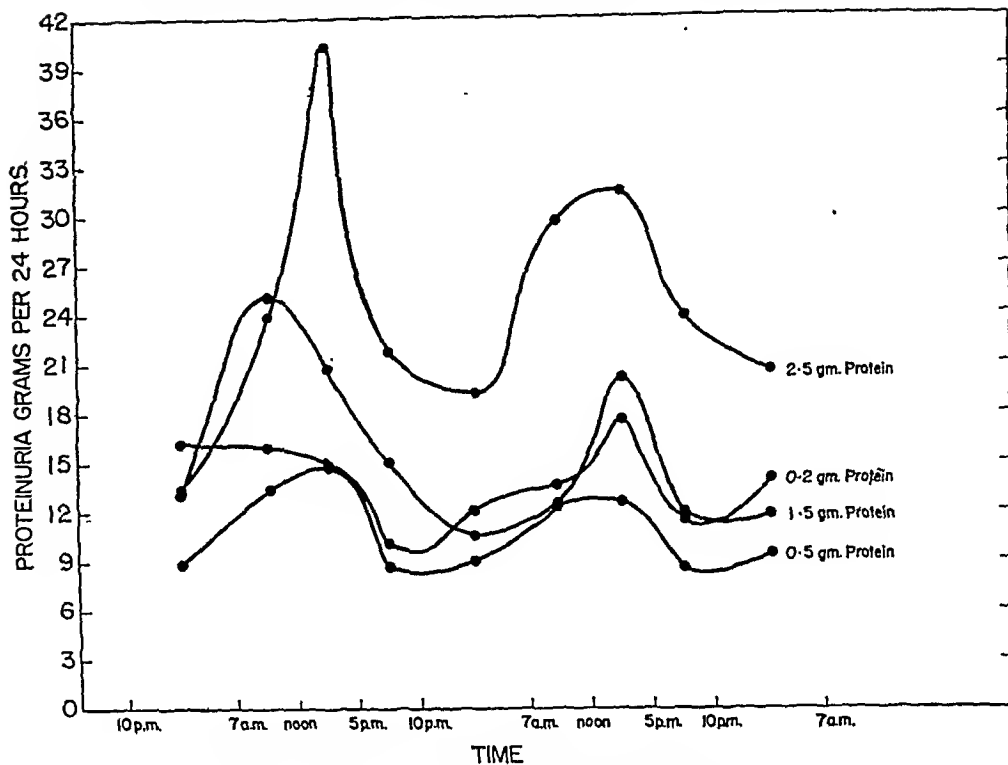


Chart 3 (case 1).—Diurnal variations in proteinuria.

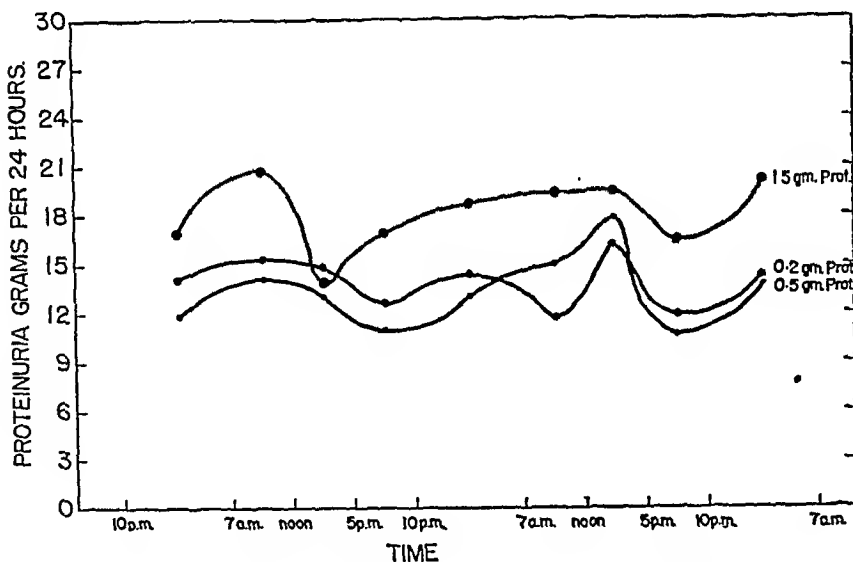


Chart 4 (case 2).—Diurnal variations in proteinuria.

investigators excreted large amounts of protein while they were studied, as were the 2 patients presented here. Keutmann and McCann,<sup>4</sup> however,

3. (a) Bulger, H. A.: Studies of Hypoproteinemia and Proteinuria, *J. Clin. Investigation* 14:705 (Sept.) 1935. (b) Keutmann, E. H., and Bassett, S. H.: Dietary Protein in Hemorrhagic Bright's Disease: II. The Effect of Diet on Serum Proteins, Proteinuria and Tissue Proteins, *J. Clin. Investigation* 14:871-888 (Nov.) 1935. (c) Keutmann, E. H., and Bassett, S. H.: Studies on the Mechanism of Proteinuria, *ibid.*, 16:767-776 (Sept.) 1937. (d) Berglund, H.; Scriver, W., and Medes, G.: Proteinuria and Plasma Proteins, in the *Kidney in Health and Disease*, Philadelphia, Lea & Febiger, 1935, pp. 473-530.

4. Keutmann, E. H., and McCann, W. S.: Dietary Protein in Hemorrhagic Bright's Disease: I. Effects upon Course of the Disease, with Special Reference to Hematuria and Renal Function, *J. Clin. Investigation* 11:973-994 (Sept.) 1932.

found this relationship in only 2 of 4 patients, and the increases in proteinuria during periods of high protein intake in these 2 patients were not large. Three of the 4 patients studied by them were excreting less than 1 Gm. of protein daily, and the proteinuria of the fourth patient rapidly diminished from 2 Gm. daily. Liu and Chu<sup>5</sup> measured the protein excretion in 1 of the 2 cases they discussed, and they thought that the proteinuria did not vary significantly when the dietary protein was altered. This patient was excreting over 1 Gm. of protein daily, but the study was complicated by a variety of diseases, including gonorrhea, ankylostomiasis, ascariasis, and syphilis which required weekly injections of neoarsphenamine. It is well known that proteinuria often is influenced by concurrent diseases and surgical procedures. Furthermore, when a patient excretes less than 1 Gm. of protein daily, a variation of a few hundred milligrams represents a large proportional change. These small actual differences in proteinuria in patients with glomerular nephritis in the latent stage frequently are observed, even when a constant intake of protein is maintained. It is thought that such factors may have obscured the influence of consumption of food protein on proteinuria in these experiments. Without presenting adequate proof, Epstein<sup>6</sup> has stated that increasing dietary protein does not result in an augmented proteinuria.

The rise in proteinuria which follows an elevation in protein intake has been attributed to an increase in glomerular filtration which occurs when the dietary protein is increased.<sup>3bc</sup> Keutmann and Bassett<sup>3c</sup> induced such an effect by administering theobromine and urea as diuretic drugs. It is generally thought that diseased glomeruli allow serum protein to leak out through abnormal "pores" of various sizes, and that an increased renal blood flow presents more blood to these "pores." In this way, it is supposed that more protein will be filtered and increased proteinuria will be produced. While this explanation may be valid, additional factors may be involved. Since the observations of Ekehorn<sup>7</sup> and Richards, Bordley and Walker,<sup>8</sup> much evidence has accumulated to show that normal glomerular filtrate contains protein, and

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5. Liu, S. H., and Chu, H. I.: An Optimal Diet in Promoting Nitrogen Gain in Nephrosis, *J. Clin. Investigation* **14**:293-303 (May) 1935.

6. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, *Am. J. M. Sc.* **163**:167-186 (Feb.) 1922.

7. Ekehorn, G.: Principles of Renal Function, *Acta med. Scandinav.*, 1931, supp. 36, pp. 1-717.

8. Richards, A. N.; Bordley, J., III, and Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine, *J. Biol. Chem.* **101**:179-191 (June) 1933.

9. Walker, A. M., and Oliver, J.: Methods for Collection of Fluid from Single Glomeruli and Tubules of Mammalian Kidney, *Am. J. Physiol.* **134**:562-579 (Oct.) 1941. Addis, T.: Proteinuria, *Tr. A. Am. Physicians* **57**:106-108, 1942.

that protein is reabsorbed by the tubule cells. This hypothesis is based on physiologic,<sup>9</sup> morphologic<sup>10</sup> and clinical data.<sup>11</sup> Dock,<sup>12</sup> Gérard<sup>13</sup> and Oliver<sup>14</sup> have discussed this subject further. Therefore, it seems reasonable to suppose that the changes in proteinuria which occur when the dietary protein is altered are dependent not only on glomerular permeability and the rate of glomerular filtration, but also on the rate of tubular reabsorption of protein.

The delay in attainment of maximum change in proteinuria after the dietary protein is altered, or the lag effect, has been noted before by Keutmann and Bassett.<sup>3b c</sup> This effect is in contrast to the immediate increase in proteinuria which follows the intravenous administration of plasma protein. The investigations of Addis, Poo, and Lew<sup>15</sup> indicate that within the body there is protein which is readily available for use under certain conditions. Keutmann and Bassett suggested that ingested protein first must be converted to a form from which plasma protein may be synthesized, presumably in depots of labile protein. The necessary time for this to occur, and then to be reflected in a change in the rate of excretion of protein, was offered as an explanation for the lag effect. Since the concentration of plasma protein remains unchanged, may it not be supposed that an equilibrium exists between the level of food protein consumed, the activity of the mechanism by which plasma protein is made and the rate of excretion of protein in the urine?

The diurnal variations in proteinuria noted in these experiments were similar to those observed by Keutmann and Bassett,<sup>3c</sup> an increased proteinuria occurring during the waking hours. These variations probably arise because of simultaneous changes in renal blood flow, due to changes in posture, activity, body temperature, ingestion of food and fluid and other factors.

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10. Randérath, E.: Die Entwicklung der Lehre von den Nephrosen in der pathologischen Anatomie, *Ergebn. d. allg. Path. u. path. Anat.* **32**:91-140, 1937. Smetana, H., and Johnson, F. R.: The Origin of Colloid and Lipoid Droplets in the Epithelial Cells of the Renal Tubules, *Am. J. Path.* **18**:1029-1046 (Nov.) 1942.

11. Addis, T.: Renal Degeneration Due to Protein Reabsorption by the Kidney, *Stanford M. Bull.* **3**:67-69 (May) 1945.

12. Dock, W.: Proteinuria and Associated Renal Changes, *New England J. Med.* **227**:633-636 (Oct. 22) 1942.

13. Gérard, P.: Comparative Histophysiology of the Vertebrate Nephron, *J. Anat.* **70**:354-379 (April) 1936.

14. Oliver, J.: New Directions in Renal Morphology: Method, Its Results and Its Future, in *The Harvey Lectures, 1944-1945*, Lancaster, Pa., Science Press Printing Company, 1945, pp. 102-155.

15. Addis, T.; Poo, L. J., and Lew, W.: Protein Loss from Liver During a Two Day Fast, *J. Biol. Chem.* **115**:117-118 (Aug.) 1936.

16. Footnote 3a and b. Footnote 4.



The lack of change in the concentration of serum protein during these experiments corroborates the findings of many other investigators.<sup>16</sup> McDonald, Corcoran and LeFevre have noted that a high protein diet cannot be expected to correct that part of the hypoproteinemia due to the underlying renal lesion.<sup>17</sup> Nevertheless, Epstein<sup>6</sup> and more recently Peters and his associates<sup>18</sup> have suggested high protein diets for the treatment of nephritis, supposing that the concentration of serum protein might rise eventually. This concentration sometimes does rise during the course of the disease, but it may also fall, and this change is independent of the level of food protein consumed, providing that this level represents an adequate amount. In patients on a constant protein intake, a change in the concentration of serum protein may be associated with the advent of some infectious disease, with a change from one stage in the disease to another, and it may sometimes occur inexplicably. These facts are abundantly supported by much experimental evidence and are attested to by everyday experience in the clinic for renal disease of this hospital.

The cause of the hypoproteinemia still is not understood completely. Linder and his collaborators found that hydremic plethora does not occur in nephritis, and that the low concentration of serum protein cannot be accounted for by dilution.<sup>19</sup> The loss of protein in the urine obviously imposes an abnormal burden on the process by which plasma proteins are produced, but it does not appear to be solely responsible for the hypoproteinemia. This opinion is in accord with the conclusions of Bloomfield,<sup>20</sup> who reviewed various clinical and experimental conditions associated with hypoproteinemia. Using a mixed diet low in protein, he was unable to induce a lasting hypoproteinemia in rats, even though they lost weight and showed signs of malnutrition. If the diet is adequate in its various components, it cannot be supposed that the low concentration of serum protein reflects a deficiency state. Defective absorption of protein from the gastrointestinal tract has not been proved. Abnormal formation of protein, however, may occur.

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17. McDonald, R. H.; Corcoran, A. C., and LeFevre, F.: Edema: III. Treatment, *Cleveland Clin. Quart.* **14**:20-27 (Jan.) 1947.

18. Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P. N., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VI. Serum Proteins in Nephritic Edema, *J. Clin. Investigation* **10**:941-973 (Oct.) 1931.

19. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, E.: Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, *J. Exper. Med.* **39**:921-929 (June) 1924.

20. Bloomfield, A. L.: The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, *J. Exper. Med.* **57**:705-720 (May) 1933.

21. Footnote 18. Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P. M., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: IX. Serum Proteins in the Terminal Stages of Renal Disease, *J. Clin. Investigation* **11**:113-122 (Jan.) 1932.

Muscular wasting is often associated with renal disease,<sup>21</sup> even when more than enough calories and protein are supplied in the diet. It is generally believed that the drop in the concentration of serum protein is mainly at the expense of the albumin fraction. Changes in the globulin fraction also have been observed.<sup>22</sup> Jameson<sup>22b</sup> has demonstrated electrophoretically that the serum of patients in the degenerative stage of glomerular nephritis contains a protein fraction which does not occur in normal serum. It seems likely that protein metabolism, particularly the mechanism for production of plasma protein, is altered qualitatively and quantitatively. The hypoproteinemia, the production of unusual plasma protein fractions and the muscular wasting all may depend partly on changes in the rate of protein synthesis and changes in the quality of the proteins synthesized.

#### THERAPEUTIC IMPLICATIONS

The dietary treatment of glomerular nephritis has evoked much discussion in the past. It has been demonstrated here, as well as in other investigations, that a higher than adequate protein intake does not elevate the serum protein concentration, and that it does increase the rate of excretion of protein in the urine. The increased proteinuria is accompanied by an increase in urea clearance<sup>23</sup> and is thought by some to be harmless to the kidneys. It may, however, further tax the protein reabsorptive ability of the tubule cells, this capacity already having been exceeded. Furthermore, an added burden may be placed on the mechanism for the production of plasma proteins, which also may be functioning imperfectly under stress.

When more dietary protein is consumed than can be utilized for anabolic purposes, the excess is deaminized to form urea. Borsook and Winegarden,<sup>23</sup> Addis,<sup>24</sup> and Newburgh<sup>25</sup> have shown that kidney work is dependent preponderantly on the urea content of the urine. The value

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22. (a) Kendall, F. E.: Studies on Serum Proteins, *J. Clin. Investigation* **16**:921-931 (Nov.) 1937. (b) Jameson, E.: Serum Protein Changes Occurring in Degenerative Stages of Bright's Disease, *Proc. Soc. Exper. Biol. & Med.* **36**:808-812 (June) 1937.

23. Borsook, H., and Winegarden, H. M.: The Work of the Kidney in the Production of Urine, *Proc. Nat. Acad. Sc.* **17**:3, 1931.

24. Addis, T.: The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, *Tr. A. Am. Physicians* **55**:223-229, 1940; The Treatment of Chronic Renal Insufficiency, *J. Urol.* **41**:126-136 (Feb.) 1939.

25. Newburgh, J. D.: The Changes Which Alter Renal Osmotic Work, *J. Clin. Investigation* **22**:439-446 (May) 1943.

26. Addis, T.: *Glomerular Nephritis*, New York, The Macmillan Company, 1948. Lippman, R. W., and Persike, E. C.: The Ambulatory Management of Azotemia and Clinical Uremia, *Arch. Int. Med.* **80**:579-586 (Nov.) 1947.

of reducing kidney work to a minimum in conditions associated with loss of nephrons has been demonstrated repeatedly, both in patients<sup>26</sup> and in experimental animals.<sup>27</sup> The concentrations of urea and creatinine in the serum frequently are used as indexes of renal failure. The complete data will be reported later, but average values for these substances and their relation to different levels of consumption of food protein for the 2 patients described here are presented in the table. These figures clearly show that increasing the consumption of food protein served to elevate the serum urea and creatinine concentrations, and thus induced an intensified azotemia.

In view of these considerations, it seems not only logical but necessary to prescribe not more than the minimum adequate amount of dietary protein. Formerly, the accepted figure was 1 to 1.5 Gm. of protein per kilogram of body weight per day. Sherman and his associates,<sup>28</sup> however, have established the requirement to be 0.5 Gm. per kilogram of body weight per day, and Hegsted and others<sup>29</sup> have given evidence that it may be even lower. For these reasons, we believe that patients who have lost renal tissue should eat a minimum but adequate amount of protein, and that as a rule this quantity should consist of 0.5 Gm. of protein per kilogram of body weight per day, plus an increment equal to that amount of protein lost in the urine.

#### SUMMARY

1. The proteinuria and the concentrations of serum protein of 2 patients in the degenerative stage of glomerular nephritis were compared in their relation to different levels of consumption of food protein.

2. Increasing the protein intake augmented the proteinuria but did not change the concentration of serum protein.

3. The significance of these effects and their therapeutic implications are discussed.

4. In conditions associated with loss of renal tissue, a diet containing a minimum but adequate amount of protein is recommended.

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27. Addis, T.; Barrett, E.; Lew, W.; Poo, L. J., and Yuen, D. W.: Danger of Intravenous Injection of Protein Solutions After Sudden Loss of Renal Tissue. *Arch. Int. Med.* **77**:254-259 (March) 1946. Farr, L. E., and Smadel, J. E.: Influence of Diet on the Course of Nephrotoxic Nephritis in Rats, *Proc. Soc. Exper. Biol. & Med.* **36**:472-473 (May) 1937; Effect of Dietary Protein on the Course of Nephrotoxic Nephritis in Rats, *J. Exper. Med.* **70**:615-627 (Dec.) 1939.

28. Sherman, H. C.; Gillett, L. H., and Osterberg, E.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, *J. Biol. Chem.* **41**:97-109 (Jan.) 1920.

29. Hegsted, D. M.; Tsongas, A. G.; Abbott, D. B., and Stare, F. J.: Protein Requirements of Adults, *J. Lab. & Clin. Med.* **31**:261-284 (March) 1946.

## COMPLEMENT FIXATION REACTIONS IN PSITTACOSIS

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BETHESDA, MD.

**D**URING the course of investigations on the psittacosis-lymphogranuloma venereum group of diseases, an opportunity was afforded to test the fixation of complement in a number of samples of serum in the presence of psittacosis antigen. These samples were submitted by practicing physicians from patients suspected of having psittacosis. For persons whose serum reacted positively, clinical and epidemiologic data were requested and additional serum specimens tested when possible. The results of the complement fixation studies supplemented by the clinical and epidemiologic data form the basis of this report on 21 cases, the disease in none of which was fatal.

Psittacosis is a severe acute infectious disease manifesting itself principally as pneumonitis and characterized by headache, malaise, dry nonproductive cough, chills and usually physical signs of pneumonia. It is contracted by association with birds of various species, chiefly those of the parrot group and pigeons, which are infected with the specific virus. Although the disease usually occurs sporadically or in small household outbreaks, in 1929-1930 an unusual number of cases was reported throughout the world, with a recorded fatality rate of 17 to 36 per cent.<sup>1</sup> The disease contracted from pigeons or nonpsittacine birds sometimes is called "ornithosis"<sup>2</sup> and is similar clinically to psittacosis, but in experimental animals the pigeon virus appears to show some slight differences from strains recovered from parrots.<sup>3</sup> In the laboratory, psittacosis virus can be recovered by injecting into white mice inoculums of the sputum, organs and occasionally the blood of persons ill or dead of the disease. The characteristic clusters of elementary bodies (L.C.L. bodies) are seen in the infected organs of animals or human beings when stained with Giemsa's or Machiavello's stain. Antibodies are produced

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From the Division of Infectious Diseases, National Institute of Health.

1. Meyer, K. F.: The Ecology of Psittacosis and Ornithosis, *Medicine* **21**:175, 1942.

2. Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, *Proc. Soc. Exper. Biol. & Med.* **49**:609, 1942.

3. Beck, M. D.; Eaton, M. D., and O'Donnell, R.: Further Laboratory Studies on the Classification of Psittacosis-Like Agents, *J. Exper. Med.* **79**:65, 1944.

in the patients' serum which can be detected by the complement fixation test as first described by Bedson<sup>4</sup> and developed further by others.<sup>5</sup> It is noteworthy that because of a common group antigen, serum from persons infected with lymphogranuloma venereum fixes complement in the presence of psittacosis and other antigens of this group. Therefore, the complement fixation reaction, while specific for the group, cannot be differentiated in the different diseases caused by the various viruses of the group.<sup>6</sup>

In the differential diagnosis, psittacosis must be distinguished from primary atypical pneumonia, which it resembles in its clinical manifestations, although it is usually severer. Recovery of the psittacosis virus from the patient or serologic evidence is the only reliable differentiation between them. Q fever of rickettsial origin also resembles psittacosis in its milder form and can be distinguished by virus isolation or specific serologic reactions. Other acute infections, such as influenza, typhoid and bacterial bronchopneumonia, are more easily recognized on clinical evidence, though often confused with psittacosis. The specific diagnosis of psittacosis is particularly important because of the apparent efficacy of penicillin in the treatment of the disease.<sup>7</sup> The unqualified laboratory diagnosis of psittacosis can be made only by the isolation from the patient and identification of the specific virus. Since the opportunity for such studies is not always available, the complement fixation reaction, when carefully interpreted, is useful in furnishing a basis for a diagnosis of reasonable certainty.

In this series of cases, the complement fixation tests were performed with an antigen prepared from the yolk sac or the allantoic fluid of the developing chick embryo infected with a strain of psittacosis virus isolated from a parrot in the laboratory of the United States Public Health Service. Yolk sac antigen was prepared by extracting with ether

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4. Bedson, S. P.: The Use of the Complement-Fixation Reaction in the Diagnosis of Psittacosis, *Lancet* **2**:1277, 1935.

5. Meyer, K. F., and Eddie, B.: The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, *J. Infect. Dis.* **65**:225, 1939. Smadel, J. E.: Atypical Pneumonia and Psittacosis, *J. Clin. Investigation* **22**:57, 1943.

6. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, *Proc. Soc. Exper. Biol. & Med.* **48**:528, 1941.

7. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Psittacosis, *Proc. Staff Meet., Mayo Clin.* **19**:204, 1944. Kirkwood, T.: Human Ornithosis: Report of a Case Treated with Penicillin, *Illinois M. J.* **90**:193, 1946. Rosebury, T.; Ellingson, H. V.; Meikeljohn, G., and Schabel, F.: A Laboratory Infection with Psittacosis Virus Treated with Penicillin and Sulfadiazine, and Experimental Data Bearing on the Mode of Infection, *J. Infect. Dis.* **80**:64, 1947.

a 10 per cent saline suspension of heavily infected yolk sacs treated with formaldehyde. The aqueous phase was used as antigen. Allantoic fluid antigen was obtained by cultivating the virus in the allantoic fluid, concentrating the formaldehyde-killed virus ten times by centrifugation and resuspending in 0.85 per cent sodium chloride solution. The technic of fixation was that used by Bengtson<sup>8</sup> for rickettsial antigens, including fixation at 37 C. for one hour. The antigens were of several lots, but all were standardized against a standard pool of serum which gave a positive reaction. Serum samples were tested quantitatively in twofold dilutions, in order to detect the highest dilution in which complete (4 plus) or almost complete (3 plus) fixation occurred in the presence of psittacosis antigen. Samples taken from the same patient at different times were tested together in parallel tests when possible.

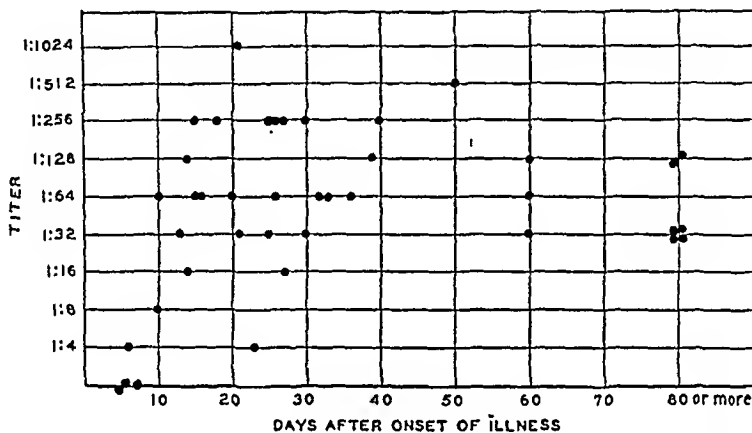


Chart showing complement fixation titers in the serum of 21 patients with psittacosis.

On the basis of significant complement fixation reactions, two groups, totaling 21 cases, were selected from the records of persons whose serum had yielded positive results. These patients presented the clinical features of psittacosis and were reported to have had intimate association with birds. One group was composed of 9 patients whose serum showed a fourfold or greater rise in titer during the course of the illness.<sup>9</sup> The second group was comprised of 12 persons whose serum had a significant titer (1 to 32) when it was first secured ten days, or later, after onset. In order to reduce the chance of including a person previously infected with lymphogranuloma venereum, no person was included for whom a history of venereal disease was obtained or whose serum was known to react positively to tests for syphilis. A summary of the clinical, epi-

8. Bengtson, I. A.: Complement Fixation in the Rickettsial Diseases Technique of the Test, Pub. Health Rep. 59:402, 1944.

9. The virus was isolated in 1 case.

Case	Patient	Color	Sex	Age (Yr.)	Contact with Birds	Highest Noted Temperature (F.)	Duration of Fever (days)	Principal Signs and Symptoms Reported	Roentgenogram of Chest	Leukocyte Count (per Cu. Mm.)	Complement Fixation Reaction of Serum		Virus Isolation
											Days After Onset	Highest Positive Dilution	
1	R.B.	W	M	55	Kept parakeets; 1 died 1 week prior to onset	102	12	Rales in base of lung, chills, pain in chest, headache, slight cough	Not taken	..	5 13	0 1:32	From patient's sputum on fifth day; unsuccessful on ninth day
2	T.D.A.	W	F	45	2 canaries died	105	60	Consolidation of lung, bradycardia	Pneumonia	10,000 and under	23 32 677	1:4 1:64 1:128	Not attempted
3	S.B.	W	F	53	Patient killed sick English sparrow 2 weeks prior to onset	102.5	6	Rales in base of lungs, pain in chest, chills, sweats, headache	Density at base of left lung and increased hilar shadow		90 days prior to onset 27	0 1:16	Not attempted
4	I.C.	W	F	55	Kept parakeets; none reported sick	101	22	Chills, weakness, anorexia	Peribronchial thickening on fifth day	9,000 8,000	7 21 315	0 1:1024 1:32	From 1 of 2 well parakeets owned by patient
5	P.C.	W	F	17	Pet parakeets (2) died 1 and 3 weeks prior to onset	103	13	Headache	Not taken	6,500	5 14 30	0 1:16 1:32	Not attempted
6	S.S.	W	M	28	Used pigeons as targets in training dogs	105	14	Headache, malaise, sweating	Pneumonitis right hilum	7,000 9,000	10 18	1:8 1:256	Not attempted
7	H.C.	W	M	66	Caught and killed wild pigeons 2 weeks prior to onset	101	19	Headache, malaise, non-productive cough	Reported as normal on thirteenth day of illness	6,300	21 39	1:32 1:128	Not attempted
8	A.W.O.	W	F	..	Parakeets purchased 2 to 3 weeks prior to onset	...	..	Malaise, rales at base of right lung	Infiltration of lower lobe of right lung	..	5-7 14-16 19-21	1:4 1:64 1:64	Not attempted
9	J.W.	W	M	..	Kept pigeons; 1 died prior to onset	103	14	Malaise, anorexia, non-productive cough; consolidation right lower part of chest	Consolidation middle and lower lobe of right lung	5,000 8,000	1-7 130	1:32 1:228	Not attempted
10	J.C.	C	F	57	Kept parakeets and parrots; none reported sick	101	25	Headache, stiff neck, thoracic pain, slight cough	Reported as normal	..	25 32 36	1:32 1:64 1:64	Not attempted

11	R.K.	W	M	41	Raised pigeons; some were sick	..	21	Malaise, cough, sweats, splenomegaly, rales at base of lungs	Reported as normal	4,800 3,350 3,000 3,750 5,850	20	1:04	Unsuccessful from pigeons
12	C.K.	W	M	38	Raised pigeons; some were sick	...	21	Cough, joint pains, sweats	Thickening of hilar region	0,000	10 26	1:04 1:04	Unsuccessful from pigeons
13	L.P.	W	F	73	2 pet parakeets died 1 week prior to onset	100.4	17	Fever, headache	Not reported	0,500	15	1:04	Not attempted
14	R.P.	W	M	27	Parakeets sold at place of employment; 1 died 3 days prior to onset	104.8	0	Cough, dyspnea, rales throughout chest	Extensive mottling throughout chest	6,100 11,300 9,200	60 230	1:128 1:32	Not attempted
15	A.S.	W	M	..	Pigeons kept near home	103.5	18	Malaise, cough, dull to percussion in right side of chest	Pneumonitis, right side of chest	...	180	1:32	Not attempted
16	C.W.	W	F	35	Pigeons kept at home	104.2	28	Cough, consolidation right upper part of chest, general rales	Consolidation upper lobe of right lung	4,000 4,100	25 40	1:250 1:250	Not attempted
17	B.A.	C	M	43	2 home-bred pigeons died	104.4	17	Minimal consolidation base of lungs, bradyarrhythmia, headache, pleuritic pain	Patchy infiltration of lower lobes	5,200 to 9,200	27 50	1:250 1:512	Not attempted
18	F.Z.	W	F	37	Kept pigeons; 2 died 5 days prior to onset	102.8	14	Headache, tachypnea, chills, sweats, rales throughout lungs	Lesion in lower part of right lung	7,750	15 30	1:250 1:250	Not attempted
19	S.A.	W	F	58	1 parakeet died prior to onset	103	..	Malaise, aching, epistaxis	Hilar shadow increased	..	14	1:128	Not attempted
20	C.J.	W	M	40	Kept parakeets; 1 died	...	..	Malaise only reported	Not reported	..	00	1:04	Virus isolated from parakeet
21	—J.	W	F	38	Kept parakeets; 1 died	..	..	Not reported	Not reported	..	00	1:32	Virus isolated from parakeet



demologic and serologic data concerning these persons is presented in the table.

All persons herein reported were over 20 years of age, and 13 of the 18 whose exact ages were known were over 40. The group included 11 women and 10 men, and 2 of the 21 were Negro. All of the patients furnished a history of intimate contact with birds: 9 with pigeons (1 of these was with wild pigeons), 9 with parakeets only, 1 with parakeets and parrots, 1 with a feral English sparrow and 1 with canaries. In 16 instances the birds were reported as being sick or dying, and virus was isolated from parakeets belonging to two households involving 3 persons.

Two family outbreaks, involving 2 brothers (cases 11 and 12) and a husband and wife (cases 20 and 21), are included in this series. In each household the onsets were almost simultaneous, suggesting the same source of infection.

The reported principal clinical features consisted of fever, sometimes with temperature as high as 105 F. and lasting usually from one to three weeks, chills, headache, cough, malaise, body ache, sweats and physical signs of pneumonia. Roentgenograms of the chest were reported in 16 cases. In 12 of these there was evidence of pulmonary lesions suggesting pneumonitis, while in 4 cases normal roentgenograms were reported. Leukocyte counts, when performed, were all under 12,000 cells per cubic millimeter. Penicillin was used in some cases and appeared to be of benefit, though the information secured for this group of cases is insufficient to evaluate critically this treatment.

The highest serum dilution fixing complement on the indicated day after onset of the disease is shown in the table. In 15 cases more than one sample was obtained at different times. Demonstrable complement-fixing antibodies usually first made their appearance from the seventh to the tenth day of illness, achieved maximum titer from the twentieth to the thirtieth day and persisted, though in decreased titer, for as long as the serum was tested. In 1 instance, antibodies were present in high titer nearly two years after recovery. Further evidence of the persistence of antibodies is furnished by my experience in 3 cases not included in the table, in which antibodies in low titer were detected four, eight, and sixteen years after the onset of the disease, the diagnosis of which had been originally confirmed in the laboratory of the United States Public Health Service.

The effectiveness of penicillin in the treatment of this frequently fatal disease necessitates a diagnosis as soon as possible and the immediate institution of treatment in persons having psittacosis. The diagnosis may be confirmed by (1) the isolation of the virus from the patient, (2) a fourfold, or greater, rise in complement-fixing antibody titer during the course of illness or (3) a high serum titer after the second week

of illness, together with a history of intimate exposure to birds suspected or known to be infected with psittacosis virus. The cross complement fixation reaction in infections caused by other members of this group of viruses, notably lymphogranuloma venereum, demands care in the interpretation of the results of the test.

#### SUMMARY

The serum complement fixation reaction, supplemented by clinical and epidemiologic data, furnished the basis for a diagnosis of psittacosis in 21 cases, the disease in none of which was fatal. A fourfold, or greater, rise in antibody titer during the course of illness occurred in the serum of 9 persons, from 1 of whom psittacosis virus was isolated. Serum from 12 persons had a significant titer (1 to 32) when it was first secured ten days, or later, after onset. All persons were reported to have manifested the clinical characteristics of the disease. However, pulmonary lesions were not demonstrated by roentgenograms of the chest in 4 of 16 persons examined. All persons reported intimate contact with birds, chiefly pet parakeets and pigeons. The serum complement fixation reaction became positive about the seventh to the tenth day after onset, achieved maximum titer about the fifteenth to the thirtieth day and persisted, though in low titer, for as long as the serum was tested (in 1 instance nearly two years).

## PAROXYSMAL COLD HEMOGLOBINURIAS

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DRESSLER<sup>1</sup> is credited with having first reported observations on a case of "paroxysmal cold hemoglobinuria," a symptom complex now known to have two separate and distinct etiologic bases. The first and more generally recognized type is syphilitic paroxysmal cold hemoglobinuria, a disease seen in a small percentage of persons with syphilis and caused by a cold-warm hemolysin unique to persons with syphilis with this disease. The second and nonsyphilitic type is cold hemagglutination paroxysmal hemoglobinuria, a disease accompanied with unusually high titers of cold hemagglutinins and first reported by Salén<sup>2</sup> in 1935 when he recorded observations on pronounced cold agglutination of the red blood cells of a nonsyphilitic patient with paroxysmal cold hemoglobinuria.

This paper will be concerned primarily with the syphilitic type of paroxysmal cold hemoglobinuria. Care was taken to avoid the error of including reports of cold hemagglutination paroxysmal hemoglobinuria in this review of cases of syphilitic paroxysmal cold hemoglobinuria. Only cases reported in sufficient detail regarding clinical and routine laboratory findings have been included.

It is the purpose of this paper to present some observations which were uncovered in this study of 37 case reports of syphilitic paroxysmal cold hemoglobinuria found in the literature since 1930. Points for differentiation between the syphilitic type and the cold hemagglutination type will be given. A new case of syphilitic paroxysmal cold hemoglobinuria treated with penicillin also will be reported, as well as observations on the effect of two of the antihistamine drugs on the cold urticaria that could be produced in this patient.

Circulating in the blood stream of patients with syphilitic paroxysmal cold hemoglobinuria is a hemolysin which, along with complement, is fixed to the red blood cells when the patient is exposed to cold. When the patient subsequently becomes warm, the hemolysin with the aid of complement hemolyzes the red blood cells, releasing hemoglobin into the

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1. Dressler, cited by Macalister<sup>3</sup> and by Mackenzie.<sup>4</sup>

2. Salén, E. B.: Thermostabiles, nicht komplexes (Auto-) Hämolysin bei transitorischer Kältehemoglobinurie, *Acta med. Scandinav.* 86:570, 1935.

stream of circulating blood. If the hemoglobinemia exceeds the renal threshold for hemoglobin, the patient will pass cherry red to dark port-wine urine.

With such episodes, the patient experiences a shaking chill often followed by fever and drenching sweats. Generalized abdominal cramps, nausea, generalized weakness, headache and backache are usual, with occasional vomiting. Some form of Raynaud's disease may occur during the paroxysm and urticarious lesions may appear. The paroxysms last for one to two hours, and after them the patient feels well again, except perhaps for some residual weakness and continued vague abdominal distress. The urine remains red or dark for four to ten hours, with urinalysis showing a positive reaction to benzidine, transient albuminuria and occasional red cells and white cells. During or shortly after the paroxysm, the blood shows transient leukopenia, which within a few hours changes to leukocytosis. Repeated attacks leave the patient weak and anemic.

#### HISTORIC OBSERVATIONS

Macalister<sup>3</sup> in 1908 and Mackenzie<sup>4</sup> in 1929 presented an excellent historical background of this disease. Briefly, according to them, Dressler in 1854 was the first to publish an account of albuminuria with dark red urine in which no red blood cells were to be found. Soon thereafter, Hassall discovered that the pigment was hemoglobin, and he and Gull in 1866 associated the paroxysms with chilling. In 1880, Rosenbach first described the cold water test which bears his name, demonstrating how it was possible to reproduce the acute paroxysm of chills and the dark urine by placing the patient's hands or feet in ice water. Kuessner in 1879 was the first to detect the hemoglobinemia which accompanied the hemoglobinuria. Murri in 1880 called attention to the association of this disease with syphilis, and Ehrlich in 1881 demonstrated that hemolysis occurred locally at the site of chilling.

#### INCIDENCE

Jones and Jones<sup>5</sup> stated that among 156,000 patients admitted to the Massachusetts General Hospital, Boston, in thirty years there were only 9 cases, and, at Peter Bent Brigham Hospital, Boston, among

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3. Macalister, G. H. K.: *The Pathology of Paroxysmal Hemoglobinuria: A Critical Review*, Quart. J. Med. 2:368, 1908-1909.

4. Mackenzie, G. M.: *Paroxysmal Hemoglobinuria: A Review*, Medicine 8:159 (May) 1929.

5. Jones, B. B., and Jones, C. M.: *Paroxysmal Hemoglobinuria*, in Nelson Loose-Leaf Living Medicine, New York, Thos. Nelson & Sons, 1920-1929, vol. 4, p. 173A.

74,186 consecutive admissions, there were only 3 cases. Howard, Mills and Townsend<sup>6</sup> found only 2 cases among 208,878 admissions in thirty-eight years at Montreal General Hospital. At the University of Chicago Clinics, there has been only 1 recognized case of syphilitic paroxysmal cold hemoglobinuria in twenty years, during which time approximately 130,000 patients were admitted to the hospital and 382,791 patients were seen in the outpatient clinics.

MECHANICS OF SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA,  
REACTION TO THE DONATH-LANDSTEINER TEST

It was not until 1904 that much was known about the mechanics of this disease. Working independently, Donath and Landsteiner,<sup>7</sup> in Vienna, and Eason,<sup>8</sup> in England, discovered the hemolysin present in the serum of patients with this disease. They demonstrated by *in vitro* tests that the hemolysin was fixed to the red cells in the cold in the presence of complement and activated to hemolyze the red cells on warming. The Donath-Landsteiner test is the name given today to this reaction. Hemolysis will be seen in a test tube containing the patient's serum, his own cells (or cells of his own type of blood) and complement. Hemolysis will not take place in the control tubes which do not contain complement nor in the tube containing normal human serum. The same hemolysis may also be demonstrated more simply by the Mackenzie rough test, in which the patient's freshly drawn whole blood is allowed to clot, then placed in ice water for ten minutes, followed by warming at 37 C. (98.6 F.) for one-half hour.

This hemolysin, the presence of which can be detected by the Donath-Landsteiner or Mackenzie rough tests, is known as the cold-warm hemolysin. It has not been demonstrated in consistent association with any disease other than syphilis. The observation of a positive reaction to the Donath-Landsteiner test in a patient with a history of paroxysms of chills and dark urine following exposure to cold can be considered pathognomonic of syphilitic paroxysmal cold hemoglobinuria.

It is important to remember that in a true, positive reaction to the Donath-Landsteiner test for syphilitic paroxysmal cold hemoglobinuria, hemolysis occurs only after the mixture of serum, cells and complement has been warmed, not before. As early as 1913, Widál, Abrami and

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6. Howard, C. P.; Mills, F. S., and Townsend, S. R.: Paroxysmal Hemoglobinuria with Report of Case, *Am. J. M. Sc.* **196:772** (Dec.) 1938.

7. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie, *München. med. Wchnschr.* **51:1509**, 1904.

8. Eason, J.: The Pathology of Paroxysmal Hæmoglobinuria, *J. Path. & Bact.* **11:167**, 1906.

Brissaud<sup>9</sup> stressed the importance of keeping the blood at a temperature of 37 C. from the time it is drawn from the patient to the time it is chilled. Blood from nonsyphilitic patients with paroxysmal cold hemoglobinuria due to high titer of cold hemagglutinins (cold hemagglutination paroxysmal hemoglobinuria) will hemolyze on exposure to cold alone without rewarming. This possible source of error in interpretation of the Donath-Landsteiner test may be responsible for some of the confusion existing in the literature concerning reports<sup>10</sup> of "paroxysmal cold hemoglobinuria" with a "positive" reaction to the Donath-Landsteiner test and a negative reaction to the Wassermann test.

York and Macfie<sup>11</sup> in 1921 showed that in the reaction to the Donath-Landsteiner test the hemolysis decreased in direct proportion to the increase in time of exposure to cold beyond seven minutes. By the end of twelve to fifteen hours, no hemolysis could be expected. Their theories concerning this behavior of the hemolysin on prolonged exposure to cold centered about depletion of available complement.

Burmeister<sup>12</sup> in 1921 concluded from his work that the hemolysin could not be distinguished or separated from the Wassermann reagin. Subsequent workers, including Smith<sup>13</sup> in 1923, Puris<sup>14</sup> and Mackenzie<sup>4</sup> in 1929 and others, consistently observed that the hemolysin is an entity distinct and separate from the reagin. This distinction can easily be

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9. Widal, F.; Abrami, P., and Brissaud, E.: *Recherches sur l'hémoglobinurie paroxystique à frigore*, Compt. rend. Soc. de biol. 65:429, 1913.

10. (a) Donath, J., and Landsteiner, K.: *Ueber Kältehämoglobinurie*, Ergebn. d. Hyg., Bakt. 7:184, 1925. (b) Ernstene, A. C., and Gardner, W. J.: *The Effect of Splanchnic Nerve Resection and Sympathetic Ganglionectomy in a Case of Paroxysmal Hemoglobinuria*, J. Clin. Investigation 14:799 (Nov.) 1935. These authors observed pronounced agglutination of their patient's red blood cells when specimens of his freshly drawn blood were exposed to room temperature, an observation which clearly puts this case in the cold hemagglutination type of "paroxysmal cold hemoglobinuria." (c) Roch, M. M., and Liengme, A.: *Hémoglobinurie paroxystique et angine érythémateuse "à frigore"*, Bull. et mém. Soc. méd. d. hôp. de Paris 46:1737, 1922. (d) Lopes, D. M.: *Hemoglobinuria paroxistica "à frigore"*, Brasil-med. 48:486 (Dec. 16-30) 1944. The author reported that in addition to obtaining a "positive" reaction to the Donath-Landsteiner test and a negative reaction of the blood to the Kahn test, he was unable to make a red blood cell count for his patient because of the extreme agglutination of the cells.

11. York, W., and Macfie, J. W. S.: *Mechanism of Autolysis in Paroxysmal Hemoglobinuria*, Brit. J. Exper. Path. 2:115 (June) 1921.

12. Burmeister, J.: *Ueber paroxysmale Hämoglobulinurie und Syphilis*, Ztschr. f. klin. Med. 92:19, 1921.

13. Smith, R. P.: *The Relationship of the Autolysin and the Wassermann Antibody in the Serum of a Paroxysmal Hemoglobinuria*, J. Path. & Bact. 26:196, 1923.

14. Puris, A. M.: *Paroxysmal Hemoglobinuria*, Am. J. Dis. Child. 37:1027 (May) 1929.

demonstrated by absorbing the hemolysin on red blood cells in the cold and quickly separating the serum. This absorbed serum will no longer hemolyze the patient's red blood cells but will still give a Wassermann reaction as strongly positive as before absorption. Maire<sup>15</sup> in 1945 discussed the transient effect of alkalis in decreasing hemolysis and hemoglobinuria.

The cold urticaria frequently seen in patients with syphilitic paroxysmal cold hemoglobinuria during an acute paroxysm is due to the action of a substance in their serum called dermolysin. This dermolysin injures the cells of the skin on exposure to cold followed by warming much the same as the hemolysin lyses the red blood cells; it is probably the same substance as the hemolysin.<sup>16</sup>

Corroborative clinical and laboratory evidence can be gained from the cold water (Rosenbach) test in which the patient's hands or feet or both are placed in ice water from fifteen to thirty minutes. After becoming warm, the patient with this disease may experience an acute paroxysm exhibiting the characteristic clinical features, including the passage of cherry red to dark urine. It has been suggested that in performing the cold water test for the first time on a patient, caution should be observed and only the hands immersed in ice water. This word of warning is well taken, for Stevenson<sup>17</sup> in 1943 reported on a patient with syphilitic paroxysmal cold hemoglobinuria who was anuric for two days after a cold water test with both his hands and feet immersed for one-half hour.

As was pointed out by York and Macfie,<sup>11</sup> repeated cold water tests may deplete the complement to such a point that a reaction may no longer be detected. It was observed of the present patient with syphilitic paroxysmal cold hemoglobinuria that his clinical reactions and the degree of hemoglobinuria following the cold water test varied from day to day. In the evaluation of any form of therapy by means of the patient's reactions to cold water tests, these variations and fluctuations should be kept in mind.

#### REPORT OF A CASE OF SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA

F., 56 years of age, white male maintenance worker, was first seen at the Albert Merritt Billings Hospital, of the University of Chicago, on May 18, 1946, with the

15. Maire, E. D.: Paroxysmal Hemoglobinuria Due to the Cold Hemolysin: Observations with a Report of a Case of Its Occurrence in an Aerial Gunner, *Arch. Int. Med.* **76**:292 (Nov.-Dec.) 1945.

16. Harris, K. E.; Lewis, T., and Vaughan, J. M.: Haemoglobinuria and Urticaria from Cold Occurring Singly or in Combination: Observations Referring Especially to Mechanism of Urticaria with Some Remarks upon Raynaud's Disease, *Heart* **14**:305 (March) 1929.

17. Stevenson, I. P.: Paroxysmal Hemoglobinuria with Report of a Case, *McGill M. J.* **12**:192 (Oct.) 1943.

complaint of abdominal pain, a loss in weight of 15 pounds (6.8 Kg.) and constipation for one year. The abdominal pain was vague, dull and aching in character and generalized over the mid and lower portions of the abdomen; it was not associated with meals or emotional stress, nor was it relieved by anything specific. He had noted some increased fatigability and a loss in weight of 15 pounds in the past year, though his appetite was still good. One month before his admission, he stated he passed bloody urine, with chills, sweating, tingling in hands and feet, malaise and weakness which came on after he was outdoors on a cold, damp day. This was the first time he had ever been aware of such an attack. There was no history of cold urticaria or cyanosis.

The family history gave no suggestion of syphilis. The past history<sup>18</sup> revealed that the patient had gonorrhea at 19 years of age, but no history of chancre, rash or other signs of acquired syphilis was obtained.

Physical examination revealed the blood pressure to be 140 systolic and 80 diastolic. The temperature was 37 C. (98.6 F.); pulse rate was 96 and regular, and the respirations numbered 18 per minute. The patient appeared chronically ill. The skin was clear. The pupils were regular and equal and reacted to light and accommodation. In the left lobe of the thyroid gland was a stony hard nodule the size of a walnut. The remainder of the gland was moderately enlarged, and no bruit was heard. The lungs were clear; the heart was normal. A few, small, subcutaneous lipomas were felt over the abdominal wall; no organs or other masses were palpable. Genitourinary organs were normal. The extremities showed no edema or gangrene. Reflexes were equal and active. There were coarse and fine tremors of the head and extended hands; the gait was normal.

Laboratory studies of the blood revealed 3,790,000 red blood cells per cubic millimeter, 12 Gm. hemoglobin per hundred cubic centimeters and 9,000 white blood cells, with 60 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes, 13 per cent monocytes and 3 per cent eosinophils. Urinalysis revealed 3 to 4 white blood cells per high power field, a trace of albumin and no red blood cells.

The blood type was ORh negative. Red blood cells showed normal fragility. The blood was negative for cold isoagglutinins. Sternal puncture showed moderate hyperplasia of the normoblastic series. Gastric analysis revealed the presence of free acid after administration of histamine. The stools showed no occult blood with the patient on a diet free from meat. Nonprotein nitrogen measured 27 mg.; plasma proteins totaled 7.82 Gm., with 4.21 Gm. albumin and 3.61 Gm. globulin, per hundred cubic centimeters. Serum cholesterol totaled 240 mg., with 173 mg. cholesterol esters per hundred cubic centimeters. Basal metabolism rate on June 11 was +20 per cent and on June 29 +34 per cent. On June 30 administration of strong iodine solution U.S.P., 10 drops three times a day, was started. On July 6 the rate was +6 per cent; on July 19 subtotal thyroidectomy was performed, with the pathologic diagnosis of adenomatous goiter with calcified shell of left lobe and hyperplasia of isthmus. On August 3, basal metabolic rate was -18 per cent.

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18. Dickson, J. G.: Paroxysmal Hemoglobinuria with Report of Case Followed for Thirteen Years, U. S. Nav. M. Bull. 34:300 (July) 1936. This report of syphilitic paroxysmal cold hemoglobinuria is demonstrative of the well recognized difficulty of obtaining a positive history of syphilis. Though the patient, a 40-year-old man, repeatedly denied any history of chancre, rash or antisyphilitic therapy, a check on his Naval hospital record showed that while in the United States Navy twenty-one years before he had been admitted to sick bay with a secondary syphilitic eruption and had received antisyphilitic therapy.



Roentgenographic examinations of esophagus, stomach, duodenum, terminal part of the ileum and the colon showed them to be normal. Intravenous pyelogram revealed nothing abnormal. Roentgenogram of the chest showed pulmonary fields to be clear, with calcification in the left lobe of the thyroid gland.

On the electrocardiogram the QRS complex was broad and slurred and at the lower limits of normal amplitude in the leads on the limbs. The T-Cf wave was at the upper limit of normal.

Five serologic determinations were made between May 18 and September 8; reactions to the Wassermann and the Kahn tests were strongly positive (4 plus for each test).

Cerebrospinal fluid was obtained under normal pressure. No cells were seen on examination. To the Wassermann and Kahn tests reactions were negative, and protein measured 38 mg. per hundred cubic centimeters. The results of the colloidal gold curve test were normal.

The Donath-Landsteiner tests received repeatedly positive reactions at serum dilutions of 1:1 and 1:2. The reactions to the Mackenzie rough tests were repeatedly strongly positive. For the first cold water test, the patient's hands were allowed to remain in ice water for ten minutes. No reaction occurred, and the urine remained light and clear. On the second test the hands and feet were placed in ice water twenty minutes. The reaction was positive, with a shaking chill followed by elevation in temperature up to 101 F., cyanosis of lips and ear lobes, blanching of finger tips and fingers, headache, nausea and generalized abdominal distress. Forty-five minutes after removal of hands and feet from ice water, the patient passed cherry red urine with a strongly positive benzidine reaction, showing 0 to 2 red blood cells and 5 to 10 white blood cells per high power field and a 1 plus reaction for albumin in a centrifuged specimen. The patient felt perfectly well two hours after completion of the test, but hemoglobinuria persisted for eight hours. Electrocardiograms taken during and two hours after the paroxysm showed no change from that made on his admission to the hospital. The white blood cell count rose from 8,800 to 13,000 four hours after conclusion of the paroxysm from the cold water test. An ice water enema retained for three minutes produced severe abdominal cramps, no hemoglobinemia and no hemoglobinuria.

Special laboratory work gave the following results:

Serum from which the hemolysin had been absorbed by exposure of 10 cc. of the patient's whole blood to 0 C. (32 F.) for seven minutes gave strong 4 plus Wassermann and Kahn reactions but negative cutaneous reactions to tests for the dermolysin. No hemolysin was demonstrable in cerebrospinal fluid. Just as much hemolysis was detectable grossly when the patient's whole blood was exposed to 0 C. for one minute (followed by one-half hour at 37 C.) as when it was exposed to 0 C. for seven minutes and thirty minutes, slightly less hemolysis when exposed for sixty minutes, appreciably less at three hours, faint hemolysis at eight hours and no hemolysis after his whole blood was exposed to 0 C. for twelve hours followed by exposure at 37 C. for one-half hour (supporting evidence for the results and concept of York and Macfie<sup>11</sup>).

Chilling of freshly drawn whole blood at 20 C. (68 F.) began fixation of complement and hemolysin to red blood cells, which was complete at 15 C. (59 F.); no hemolysis was observed when the blood was chilled to only 25 C. (77 F.), followed by exposure to 37 C. for one-half hour. Consistently greater hemolysis was noted when the patient's serum was used with cells of normal persons in the same blood group (0) than when the patient's own cells were used. When cells of the other blood groups were used, no hemolysis or only slight hemolysis was detected;

no more was seen than one would expect from the combined agglutination and hemolytic reaction of incompatible serums and cells.

#### REVIEW OF CASE REPORTS PUBLISHED SINCE 1930

The literature was surveyed back to and including 1930 for reports of cases of syphilitic paroxysmal cold hemoglobinuria sufficiently detailed to include a history and results of physical examination, the Donath-Landsteiner test, serologic tests for syphilis and routine laboratory work. Thirty-seven such case reports were available in the literature. Many of the reports appeared in foreign journals, a few of which were not obtainable owing to the recent international crisis. The pertinent information found in these 37 reports is summarized in table 1 and analyzed in table 2, which is self explanatory. These tables will be referred to in the subsequent discussion on etiology and immunity. Included in the interpretive review is the present case report of patient F.

#### ETIOLOGIC ASPECTS AND THE ROLE OF SYPHILIS

Murri<sup>19</sup> in 1885 was the first to point out a relation between cold hemoglobinuria and syphilis. Since that time, almost all students of this disease have upheld his conclusion and have emphasized the role of syphilis in the etiology of cold hemoglobinuria due to the cold-warm hemolysin. Despite the unanimity of opinion prevailing in the literature, some doubt still remains as to the syphilitic nature of this disease, and some consideration is still given to the notion that the positive serologic reactions seen in these patients are false positive reactions. This consideration is no longer justified. Probably the one factor most responsible for the unwillingness of some workers to accept the syphilitic basis for this disease is the customary absence of clinical manifestations of active syphilis. This apparently paradoxical situation could be interpreted in terms of immunity, as will be discussed later, and it should not be held up as evidence against a syphilitic origin.

The records of children with hemoglobinuria due to the cold-warm hemolysin strongly indicate that patients with this disease have at some time in the past been infected by the spirochete of syphilis. A child more than 6 months of age with persistent positive serologic reactions whose mother's reactions are also positive must be considered a syphilitic child, in spite of lack of clinical evidence of congenital syphilis.

Of the 37 case reports reviewed for this paper, 10 were of children, and all 10 children were more than 6 months of age. In 8 of these 10 cases the parents were investigated, and in each of the 8 cases a positive family incidence of syphilis was established by history, serologic reac-

19. Murri, A., cited by Mackenzie.<sup>4</sup>

TABLE 1.—*Reports of 37 Cases of Syphilitic Paroxysmal Cold Hemoglobinuria Found in the Literature Since 1930, with Report of Present Case*

Author and Reference	Age, Yr., and Sex	Serologic Reaction	History of Syphilis, Acquired or Congenital	Clinical Evidence of Active Syphilis Other Than Serologic Reactions and Cold-Warm Hemolysin*	Results of Antisyphilitic Therapy
Inamori, S.: <i>Am. J. Dis. Child.</i> 44:379 (Aug.) 1932	7 M	++++ Wassermann	Not given	None	Cured by fever therapy with Spirillum minus (and 5 injections neocarsphenamine U. S. P.)
Ito, N.: <i>Am. J. Dis. Child.</i> 46:1092 (Nov.) 1933	4 F	++++ Wassermann	Not given	None	Cured by fever therapy with Spirillum minus (and 5 injections neocarsphenamine)
Pilot, I., and Friedman, H.: <i>M. Clin. North America</i> 13:1231 (March) 1930	49 M	Strongly positive Wassermann and Kahn	Negative	None	Disappearance of hemoglobinuria but Wassermann and Kahn reactions still strongly positive
Hughes, J. F.: <i>M. J. Australia</i> 2:503 (Dec. 18) 1943	22 M	Strongly positive	Negative	None	Not mentioned
Stevens (Footnote 17)	43 M	Positive	Negative	None	Not mentioned
Woolter and Parks (Footnote 24)	30 M	++++ Wassermann, ++++ Kahn	+ Wassermann reaction 9 yr. before, treated with arsenicals	None Negative cerebrospinal fluid reaction	Disappearance of hemoglobinuria but appearance of tabetic form of dementia paralytica with positive cerebrospinal fluid reaction 1 yr. later
Mairo (Footnote 15)	26 M	Positive	Negative	None	Disappearance of hemoglobinuria; Donath-Landsteiner reaction reversed to negative
Goldberg (Footnote 31)	26 M	Strongly positive	Negative	None	Ameliorated; treatment with 3,000,000 units penicillin; still had hemoglobinuria on exposure to cold but paroxysms appeared less severe
Jedlicka, V., and Kral, J.: <i>Sang</i> 5:954, 1931	19 M 28 M	Positive Positive	Positive Negative	None None	Hemoglobinuria ameliorated Clinical cure
Huang, C. H., and Sia, R. H. P.: <i>Chinese M. J.</i> 50:214 (March) 1936	39 M	Strongly positive	Multiple venereal contact	None	Clinical cure
Jaffe, L.: <i>J. Michigan M. Soc.</i> 34:312 (May) 1935	47 M	++++ Wassermann	Gonorrhea at age 10; syphilis denied	None	Ameliorated
Bollen, K.: <i>Acta paediat.</i> (supp. 1) 17:324, 1935	5 M 11 F	Strongly positive Positive	Both parents: positive Wassermann reactions Mother: ++++ Kahn	None None	Not mentioned Not mentioned

Phillips, J. T., Jr., and Hogg, P.: Virginia M. Monthly 66:737 (Dec.) 1939	4 M	+++++ Wassermann +++++ Kahn	Mother: ++++ Wassermann	None	Not mentioned
Logue, R. G.: J.M.A. Georgia 30:275 (June) 1941	13 M	+++++ Wassermann +++++ Kahn	Mother had syphilis	None	Ameliorated
Mitacek, S.: Sang 6:153, 1932	35 M	Positive	Syphilis for 13 yr.	None	Not mentioned
Kelly, H. T.: Pennsylvania M. J. 37:393 (Feb.) 1934	33 F 10 F	Wassermann negative Strongly positive	Negative Mother had syphilis	None None	Satisfactory Satisfactory
Rosen, S. F.: South. M. J. 26:1038 (Dec.) 1933	36 M	+++++ Kahn Wassermann (anticomplementary)	Chancre 8 yr. before	None	Not mentioned
Swineford, O., Jr.: J. Lab. & Clin. Med. 16:347 (Jan.) 1931	30 M	Strongly positive	Wife has syphilis; patient had penile sore	None	Ameliorated
Agnoli, R.: Minerva med. 2:731 (Nov.) 1932	34 F	Strongly positive	Positive with secondary syphilis	None	Not mentioned
Cattaneo, L.: Gior. ital. di dermat. e sif. 72:1159 (Oct.) 1931	33 M	Very strongly positive	Positive with chancre	None	Ameliorated
Purig, Leal, J.: Arch. de med., cir. y especialid. 35:113 (Feb. 6) 1932	32 M	Positive	Positive with chancre	None	Not mentioned
Dickson (Footnote 13)	40 M	Strongly positive	Secondary syphilis with mucous patches 21 yr. before	None	Disappearance of hemoglobinuria after therapy with mercury succinimide and neocarsphenamine; clinical cure followed 13 years
Howard and associates (Footnote 6)	33 M	Strongly positive	Gonorrhea 10 yr. before; syphilis denied	None	No hemoglobinuria after 3 mo. antisyphilitic therapy; followed 1 yr.
Thurmon and Blaine (Footnote 23)	23 F 20 M 46 F	Positive Wassermann; positive Kahn; positive Hinton Positive Wassermann; positive Hinton Positive Wassermann	Mother had + Wassermann reaction Negative Patient and husband had chancre	None None None	Not given Hemoglobinuria ameliorated Hemoglobinuria disappeared; later active syphilis set in, with perforated septum and tabes; no recurrence of hemoglobinuria
d'Alessandro, G.: Riforma med. 51:1280 (Aug. 24) 1935	44 M	+ + Kahn	History of chancre	None	Not mentioned
Wassmann, K.: Ugesk. f. laeger 99:771 (July 15) 1937	3 F	Very strongly positive	Mothers serologic reaction strongly positive	None	Not mentioned

TABLE 1.—*Reports of 37 Cases of Syphilitic Paroxysmal Cold Hemoglobinuria Found in the Literature Since 1930, with Report of Present Case—Continued*

Author and Reference	Age, Yr., and Sex	Serologic Reaction	History of Syphilis, Acquired or Congenital	Clinical Evidence of Active Syphilis Other Than Serologic Reactions and Cold-Warm Hemolysin*	Results of Antisyphilitic Therapy
Moorman, E. R.: <i>Virginia M. Monthly</i> 61:14 (April) 1934	38 M	++++ Wassermann	Chancre 15 yr. before	None	Clinical cure of hemoglobinuria but Wassermann reaction still ++++
Hall, S. C., Jr., and Barksdale, E. E.: <i>Virginia M. Monthly</i> 65:126 (March) 1938	9 M	+ Wassermann, ++++ Kahn	Father; + Wassermann	None	Clinical cure
Lewis, S. J., and Fears, T. A.: <i>Texas State J. Med.</i> 32:403 (Oct.) 1936	31 F	Strongly ++++ Wassermann and Kahn reactions	Negative	None	Ameliorated
Brule, M.; Hillemand, P.; and Gaube, R.: <i>Bull. et mem. Soc. med. d. hop. de Paris</i> 53:197 (Feb. 22) 1937	55 M	Strongly positive	Negative	None	Not mentioned
McCarthy and Wilson (Footnote 21)	23 M 5 F	Strongly positive Wassermann and Kahn reactions Positive	Chancre at 17 yr. of age Mother had positive Wassermann reaction	None Interstitial keratitis	Disappearance of hemoglobinuria Disappearance of hemoglobinuria
F. (present case)	56 M	Very strongly ++++ Wassermann, ++++ Kahn	Denied	None	Clinical cure with 5,000,000 units of penicillin but still has occasional moderately positive in vivo and in vitro tests and strongly positive serologic reactions

\*"Clinical evidence of active syphilis" means clinical manifestations of invasive spirochetal activity, excluding lesions such as Hutchinson teeth and rhagades which are not active foci but old scars and degenerative residua.

tions or clinical evidence of the latent or manifest forms in parents or siblings.

There is no reason to consider that, while the positive serologic reactions in children with this disease are then admittedly true positive reactions, the positive serologic reactions in the adults are false positive the two age groups are identical symptomatically and clinically. No variation has ever been described between the nature of the cold-warm hemolysin of the child and the nature of that of the adult, or in its mechanism as studied in vitro.

TABLE 2.—*Analysis of Reports of 38 Cases of Syphilitic Paroxysmal Cold Hemoglobinuria Appearing in the Literature Since 1930 (Including Present Case).*

<i>History of Syphilis—Familial or Acquired</i>	
Negative .....	13
Positive .....	23
<i>Clinical Evidence of Active Syphilis (Besides Serologic Reaction and Cold-Warm Hemolysin)</i>	
Not mentioned .....	2
Present .....	0
Absent .....	38
<i>Serologic Reactions</i>	
"++++," "strongly positive" or "very strongly positive" .....	24
"Positive" .....	11
Doubtful, +1, ++ or +++ .....	2
"Negative" .....	1
<i>Results of Antisyphilitic Treatment</i>	
Clinical "cure" .....	15
Cold hemoglobinuria ameliorated .....	10
No success with apparently adequate treatment .....	0
Not mentioned .....	13

Another strong argument in favor of the syphilitic origin of the cold-warm hemolysin is the good response to adequate antisyphilitic therapy that can be expected in the majority of these patients, children or adults.

New and interesting evidence again implicating syphilis in the etiology of this disease comes from Neurath,<sup>20</sup> who recently worked out a technic for better differentiation between false positive and true positive serologic reactions for syphilis. Neurath observed that the serum of patient F. gave a true syphilitic type reaction. In addition, the Wassermann and Kahn reactions of this patient have remained strongly positive for two years, consistent with a true syphilitic reaction.

As shown in table 2, clinical evidence of invasive spirochetal activity was absent in each of the 38 patients with syphilitic paroxysmal cold hemoglobinuria.<sup>21</sup> Without the cold hemoglobinuria, these patients

20. Neurath, H.: False Positive Reactions in the Serology of Syphilis, J. Ven. Dis. Inform., 1945, supp. 20, p. 134.

would be considered to be in the latent stage of late seropositive syphilis, congenital or acquired. Consideration might also be given to the concept that syphilitic paroxysmal cold hemoglobinuria represents an immune state in syphilis, possibly of an unusual nature. However, the presence of the cold-warm hemolysin in the blood of 20 per cent of persons with late and latent syphilis, as observed by Kumagai and Jnoue,<sup>22</sup> in the absence of hemoglobinuria indicates that the basic mechanism producing the hemolysin is not unusual. That it was proved absent by these same workers in all 13 patients with secondary syphilis studied by them further points to the presence of the hemolysin only in the presence of immunity as it develops in the late stages. Jones and Jones<sup>5</sup> reported a positive reaction to Donath-Landsteiner test in 6.6 per cent of 45 persons with syphilis they studied. They did not mention the clinical phases of syphilis represented in their patients. Perhaps the degree of hemolysin titer parallels the degree of immunity. Syphilitic persons with hemoglobinuria have a high titer of the cold-warm hemolysin and do not present clinical manifestations of an active syphilitic infection.

Reports of cases by Thurmon and Blaine<sup>23</sup> and Woofter and Parks<sup>24</sup> are of considerable interest in such speculation. In 1931 Thurmon and Blaine reported on 3 patients with syphilitic paroxysmal cold hemoglobinuria, 1 of whom was a 46 year old woman. She and her husband had a history of chancre. On admission of the wife to the hospital on Nov. 7, 1917, examination revealed cold hemoglobinuria with positive reactions to Donath-Landsteiner tests and a positive reaction to the Wassermann test, with no other evidence of syphilis. During this stay in the hospital she received antisyphilitic therapy in the form of potassium iodide orally, mercury succinimide intramuscularly and two intravenous injections of arsphenamine U.S.P. ("diarsenol"). She was readmitted two days after her discharge, on December 20, with acute exacerbation of her cold hemoglobinuria; she received five more injections of mercury succinimide and was discharged about two weeks later. She was not seen for almost seven years, during which time she had no

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21. McCarthy, F. P., and Wilson, R., Jr.: Paroxysmal Hemoglobinuria: Report of Cases, with Familial Findings, *New England J. Med.* **207**: 1019 (Dec. 8) 1932. This case of interstitial keratitis was in a 5 year old girl who had paroxysms of cold hemoglobinuria. However, interstitial keratitis is itself an indirect result of congenital syphilis of nutritional, degenerative or allergic nature and is not caused by direct invasion of the cornea by spirochetes.

22. Kumagai, T., and Jnoue, B.: Beiträge zur Kenntnis der paroxysmalen Hämoglobinurie, *Deutsche med. Wchnschr.* **38**:361, 1912.

23. Thurmon, F., and Blaine, D.: Paroxysmal Hemoglobinuria: Observation Based upon Study of Three Cases, *Am. J. Syph.* **15**:350 (July) 1931.

24. Woofter, A. C., and Parks, B. S.: Paroxysmal Hemoglobinuria with Report of Case, *Ann. Int. Med.* **12**:402 (Sept.) 1938.

further recurrence of her cold hemoglobinuria, though she was frequently exposed to the cold. On Nov. 24, 1924, she was readmitted with dyspnea, absent ankle jerks, perforated septum and positive reaction to the Wassermann test, but she had no recurrence of her cold hemoglobinuria. Seven years later, on May 12, 1931, she still had a positive reaction to the Wassermann test but no cold hemoglobinuria.

Woofter and Parks<sup>24</sup> in 1938 reported on a patient with syphilitic cold hemoglobinuria, with positive reactions to Wassermann, Donath-Landsteiner and Rosenbach cold water tests. No other clinical evidence of syphilis was present. Antisyphilitic therapy was started, and thereafter the patient had no recurrence of his cold hemoglobinuria. However, about one year later, while the patient was receiving antisyphilitic therapy and still had positive serologic reactions, mental dulness, apathy and uneven gait developed, with diagnosis of the tabetic form of dementia paralytica, but he had no recurrence of his cold hemoglobinuria.

Apparently, in these cases the treatment was enough to upset the immune balance and depress the hemolysin but was inadequate to rid the tissues of the spirochete. With the "natural" immune state upset, important defenses of the body against further invasion by the spirochete were removed.

No cases of hemoglobinuria or of positive reactions to the Donath-Landsteiner tests in the parents of persons with congenital syphilitic hemoglobinuria are reported. Thus, there is no reason to assume that formation is the result of infection by a specific strain of *Treponema pallidum*.

#### SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA AND COLD HEMAGGLUTINATION PAROXYSMAL HEMOGLOBINURIA

It has become increasingly evident in recent years that the diagnosis "paroxysmal cold hemoglobinuria" is inadequate. Two separate and distinct disease processes capable of producing intravascular hemolysis on exposure to cold are now recognized. One is syphilitic paroxysmal cold hemoglobinuria due to a cold-warm hemolysin. The other is cold hemagglutination paroxysmal hemoglobinuria due to an abnormally high titer of cold hemagglutinins. In the breakdown of red cells due to high titers of cold hemagglutinins, no hemolysin has been demonstrated. Since Salén's description of this later condition in 1935, more and more reports of cases are appearing.<sup>25</sup> As early as 1909, Moro, Noda and

25. Ernstene and Gardner.<sup>10b</sup> Lopes.<sup>10d</sup> McCombs, R. P., and McElroy, J. S.: Reversible Auto-Hemagglutination with Peripheral Vascular Symptoms, *Arch. Int. Med.* **59**:107 (Jan.) 1937. Roth, G.: Paroxysmal Hemoglobinuria with Vasomotor and Agglutinative Features, *Proc. Staff Meet., Mayo Clin.* **10**:609 (Sept. 25) 1935. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities: Report of Case, *Arch. Int. Med.* **72**:506 (Oct.) 1943.



Benjamin<sup>26</sup> pointed out that those cold hemoglobinurias which occur in a person with a negative reaction to the Wassermann test belong in some other category, because they are not caused from syphilis.

Stats<sup>27</sup> made clear that four points must be fulfilled to demonstrate in vitro the breakdown of red cells due to a high titer of cold hemagglutinins: (1) the presence in high titer (over 1:3,000) of the cold hemagglutinin, (2) a cold-maintained environment, (3) slight agitation of the mixture of red cells and serum paralleling the trauma to which the red cells are subject in the stream of circulating blood and (4) a sufficient volume of red cells on which the cold hemagglutinin may act.

The following points of differentiation between syphilitic paroxysmal cold hemoglobinuria and cold hemagglutination paroxysmal hemoglobinuria may be summarized:

1. Cold agglutinins are absent in the syphilitic type but present in high titer (over 1:3,000) in the cold hemagglutination type. They can usually be detected by a routine red blood cell count at room temperature.

2. In the syphilitic type, the reactions to the Donath-Landsteiner or Mackenzie tests are positive; in the cold hemagglutination type, they are negative, that is, hemolysis takes place without warming or no hemolysis occurs.

3. In the syphilitic type, a positive reaction of the blood to Wassermann and Kahn tests can be considered essential for the diagnosis; in the cold hemagglutination type, a positive reaction to Wassermann or Kahn tests is practically never present, and if such a reaction is present in the absence of a positive reaction to Donath-Landsteiner, it can be considered coincidental.

4. In the syphilitic type, complement is required. Wintrobe,<sup>28</sup> in speaking of simply "paroxysmal cold hemoglobinuria," cited the reports of Ernstene and Gardner<sup>10b</sup> and Salén<sup>2</sup> as descriptions of cases not requiring complement. Both these cases were of cold hemagglutination paroxysmal hemoglobinuria, the authors observing conspicuous agglutination of red cells in routine examinations of the blood of their patients. Both these patients also had negative serologic reactions. Complement is not required in the cold hemagglutination type.

5. In the syphilitic type, a dermolysin can practically always be demonstrated. (Harris and associates<sup>16</sup> reported 1 case of syphilitic

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26. Moro, E.; Noda, S., and Benjamin, E.: Paroxysmale Hämoglobinurie und Hämolyse in Vitro, München. med. Wchnschr. 56:545, 1909.

27. Stats, D.: Cold Hemagglutination and Cold Hemolysis: Hemolysis Produced by Shaking Cold Agglutinated Erythrocytes, J. Clin. Investigation 24:33 (Jan.) 1945; Cold Agglutinated Erythrocytes: Hemolytic Effect of Shaking, Proc. Soc. Exper. Biol. & Med. 54:305 (Dec.) 1943.

28. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, pp. 429-430.

paroxysmal cold hemoglobinuria with no demonstrable dermolysin.) No reports were found of a dermolysin demonstrable in the serum of patients with the cold hemagglutination type.

6. Cold urticaria is frequently seen during the paroxysms in the syphilitic type. Stats and Wassermann<sup>29</sup> reported no authentic cases on record of cold urticaria associated directly with the paroxysm in the cold hemagglutination type.

7. In the syphilitic type the hemolysin is type specific, while the cold hemagglutinin will act on blood of other types, as well as on the blood of other animals (Stats and Wassermann<sup>29</sup>).

It is interesting that of the 2 cases of "paroxysmal cold hemoglobinuria" on record at the University of Chicago Clinics, 1 of them (the present case) was of the syphilitic type, while the other was of the type due to high titer of cold hemagglutinins. The patient with the latter type experienced severe hemolytic crises with paroxysms of hemoglobinuria after exposure to cold and had eight admissions to the hospital for transfusions. The red blood cells of this patient agglutinated so strongly at room temperatures that it was difficult to count the red cells without warming each bit of equipment with which they came in contact. When needles, syringes and test tubes were warmed, it was seen that the patient's blood was not hemolyzed if chilled without agitation then warmed (negative reaction to Donath-Landsteiner and Mackenzie tests). This patient also had repeated negative blood Wassermann and Kahn reactions. With his attacks and between attacks he experienced the same vague abdominal distress with anorexia, nausea and vomiting as experienced by patient F., who had syphilitic paroxysmal cold hemoglobinuria.

Treatment of cold hemagglutination paroxysmal hemoglobinuria is uncertain and unsatisfactory. As one would expect there are no reports of success with antisyphilitic therapy. Ernstene and Gardner<sup>10b</sup> in 1935 reported satisfactory amelioration with sympathectomy in their patient.

#### ANTI-HISTAMINE DRUGS AND THE DERMOLYSIN

In many patients with syphilitic paroxysmal cold hemoglobinuria cold urticaria develops, along with the attacks of chills and dark urine, on exposure to cold. Harris, Lewis and Vaughan<sup>16</sup> comprehensively covered this aspect of syphilitic paroxysmal cold hemoglobinuria, concluding that the dermolysin causing the urticaria is either the same substance as the hemolysin or a closely allied substance. The antibody which causes cold urticaria in these patients can be transferred passively to nonsensitive persons. If serum of the patient is injected intradermally

29. Stats, D., and Wassermann, L. R.: Cold Hemagglutination—An Interpretive Review, *Medicine* 22:363 (Dec.) 1943.

into a nonsensitive test subject and the injection site is chilled and warmed, an erythematous, pruritic wheal appears. This was demonstrated in the case of patient F. However, it was observed, that, if the hemolysin was absorbed from his serum by exposure of a tube of his whole clotted blood to the cold followed by quick centrifugation in ice-packed tubes, the dermolysin was also absorbed and no wheal could be produced by intradermal administration (and cold-warm treatment) of this absorbed serum either by injection into patient F. or by passive transfer. This would confirm the conclusions of Harris, Lewis and Vaughan that the hemolysin and the dermolysin are either the same substance or closely allied substances, and that they are independent of the Wassermann antibody.

Serum from the patient with cold hemagglutination paroxysmal hemoglobinuria and negative reactions to Wassermann and Donath-Landsteiner tests observed recently contained no such dermolysin. No wheal could be demonstrated on injection of his serum followed by the cold-warm treatment of the injection site in patient F.

When the new histamine-inhibiting drugs, such as diphenhydramine hydrochloride ("benadryl") and tripeleminamine hydrochloride N.N.R. ("pyribenzamine") became available recently, studies were made on their effect on the action of the dermolysin present in the serum of patient F. While he received large doses (300 mg. orally in eight hours) of either diphenhydramine hydrochloride or tripeleminamine hydrochloride, the action of the histamine was decidedly suppressed and much smaller urticarious wheals were raised than those obtained when he was not taking the drugs with the same technic. Besides a notable decrease in the size of the wheal, itching and erythematous flare were consistently absent. Neither diphenhydramine hydrochloride nor tripeleminamine hydrochloride had any noticeable effect on patient F.'s hemoglobinuria.

#### TREATMENT OF SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA

The treatment of choice of cold hemoglobinuria due to the cold-warm hemolysin is antisyphilitic therapy. Good results can be expected and have been reported from the use of arsenicals and the heavy metals. Kumagai and Namba<sup>30</sup> reported 10 clinical cures in 14 cases of syphilitic paroxysmal cold hemoglobinuria treated with arsenicals and heavy metals.

In the survey presented of 38 cases of syphilitic paroxysmal cold hemoglobinuria, results of antisyphilitic therapy are given in 25 of the reports. Fifteen of these cases were reported as clinically "cured" (no chills or dark urine during cold weather); 10 were reported as

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30. Kumagai, T., and Namba, M. Weitere Beiträge zur Kenntnis der paroxysmalen Hämoglobinurie, *Deutsches Arch. f. klin. Med.* 156:257, 1927.

ameliorated in severity of reaction to cold, and none were reported as resistant to reportedly adequate antisyphilitic therapy.

Since only one report<sup>31</sup> concerning the use of penicillin in the treatment of syphilitic paroxysmal cold hemoglobinuria was found in the literature, it was decided to treat patient F. with the antibiotic substance. He was given penicillin intramuscularly, 20,000 units every three hours the first two days, 30,000 units every three hours the next two days and 40,000 units every three hours thereafter, to the total dose of 5,050,000 units.

He experienced no chills or dark urine since his discharge from the hospital seven months before this report, although he was outdoors frequently in below-freezing weather. However, moderate reactions to cold water exposure tests have occasionally occurred during the past six months, with dark urine and systemic reaction, though these reactions were not as severe as those elicited before the institution of penicillin therapy. Reactions to Donath-Landsteiner and Mackenzie tests at present also remain slightly positive, and his Wassermann and Kahn reactions are both still strongly positive.

It is not intended that a course of 5,000,000 units of penicillin be recommended as definitive treatment of syphilitic paroxysmal cold hemoglobinuria. Patients with this condition have the late form of syphilis and should be followed by weekly injections of oxophenarsine hydrochloride U.S.P. ("mapharsen") and bismuth as this patient is now receiving.

#### SUMMARY AND CONCLUSIONS

1. Syphilitic paroxysmal cold hemoglobinuria is a disease characterized by sudden onset of shaking chills, fever, abdominal distress, nausea and, frequently, evidences of Raynaud's disease, associated with passage of red to dark urine for four to ten hours after exposure to cold, owing to a cold-warm hemolysin in the patient's serum which, along with complement, attaches itself to the red blood cells in the cold, hemolyzing the red blood cells on subsequent warming.

2. This cold hemoglobinuria due to the cold-warm hemolysin is a manifestation of syphilis. It has not been reported in consistent connection with or as a counterpart of any disease other than syphilis.

3. Thirty-eight case reports were reviewed, and none of them revealed clinical manifestations of invasion of tissue by *Treponema pallidum*. Theoretic possibilities of the relation of the hemoglobinuric state to a state of immunity in syphilis are discussed. It is assumed that the cold-warm hemolysin appears only during the quiescent stage of the

31. Goldberg, L. C.: Treatment of Paroxysmal Hemoglobinuria with Penicillin, *Am. J. Syph., Gonorr. & Ven. Dis.* 31:163 (March) 1947.

late form of syphilis, when owing to natural immune defenses the spirochetes are not invasive.

4. There are two separate and distinct etiologic factors which can produce the symptom complex of "paroxysmal cold hemoglobinuria"—syphilitic paroxysmal cold hemoglobinuria and cold hemagglutination paroxysmal hemoglobinuria. Points of differentiation between the two conditions are presented. For diagnostic purposes the term "paroxysmal cold hemoglobinuria" is inadequate and should be abandoned.

5. Diphenhydramine ("benadryl") hydrochloride and tripelenamine hydrochloride ("pyribenzamine") were observed to be effective in reducing decidedly the urticarious reaction produced by the dermolysin present in the serum of a patient with syphilitic paroxysmal cold hemoglobinuria. These drugs had no apparent effect on the patient's intravascular hemolysis and hemoglobinuria.

6. A typical case of syphilitic paroxysmal cold hemoglobinuria is presented, with results of special laboratory investigation. Treatment with 5,000,000 units of penicillin resulted in a clinical "cure," for the patient has experienced no chills or dark urine, although he frequently works outdoors in below freezing weather. However, he still has a moderately positive reaction to the Mackenzie test and reacts adversely on occasion to cold water tests.

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Fifty-Ninth Street and Ellis Avenue (37).

# IMPAIRMENT OF PULMONARY FUNCTION IN POLIOMYELITIS

Oximetric Studies in Patients with the Spinal and Bulbar Types

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**I**MPAIRMENT of respiration presents a serious therapeutic problem in poliomyelitis. Single or multiple involvement of the components of the respiratory mechanism frequently decreases the patient's arterial oxygen saturation in cases of the spinal and bulbar types during the acute and convalescent stages of the disease. Accurate diagnosis of the nature of the respiratory defect is an essential step in the treatment of the patient.

From a physiologic viewpoint, the various disturbances in pulmonary function in poliomyelitis may be resolved into two general types, ventilatory deficiency and alveolar deficiency. Defective ventilation may occur with paralysis of the diaphragm or of the intercostal muscles or with depression of the respiratory center. Alveolar deficiency, or inadequate gas transfer between the pulmonary alveoli and the blood, may result from parenchymal lesions in the lungs, e.g., pulmonary edema, atelectasis, focal hemorrhage and pneumonia. A similar classification was suggested in 1941 by Cournand and Richards<sup>1</sup> and more recently by Ornstein and his co-workers.<sup>2</sup> Both the ventilatory exchange and the alveolar transfer of gases may be deficient in cases of obstructive lesions of the upper airway.<sup>3</sup>

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1. Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency: I. Discussion of a Physiologic Classification and Presentation of Clinical Tests, *Am. Rev. Tuberc.* **44**:26, 1941.

2. Ornstein, G. C.; Herman, M.; Friedman, W. N., and Friedlander, E.: Pulmonary Function Tests, *Am. Rev. Tuberc.* **53**:306, 1946.

*(Footnotes continued on next page)*

Objective evaluation of impaired pulmonary function and appraisals of oxygen or respirator therapy were undertaken with the use of the Millikan-Smaller recording oximeter.<sup>4</sup> In this report the technic employed in these function studies will be presented, together with the findings in 8 patients with poliomyelitis. As a result of the application of these function studies to 43 patients during the epidemic, certain practical uses of oximetry have appeared and will be described.

## METHODS

Changes in the arterial blood oxygen saturation were measured by means of the recording oximeter. This device consists essentially of a pair of photoelectric cells fixed in a mounting which can be attached to the pinna of the ear and allows a standard light source to activate the cells after passing through the ear and two selective filters. One filter allows light to pass at the wavelength for maximum selective absorption for reduced hemoglobin, and the other allows it to pass at a wavelength at which light is absorbed by both reduced hemoglobin and oxyhemoglobin to equal extents. By a suitable electrical arrangement described by Hemingway,<sup>4c</sup> it is possible to record quantitatively the changes in the fraction of hemoglobin present as oxyhemoglobin, or in the oxygen saturation.

It should be noted that there are certain errors<sup>5</sup> which enter into such measurements, the major one of which, from a practical viewpoint, is that due to edema of the ear developing while the earpiece is in place. In these studies errors from this source were not observed in less than three hours of use. Therefore continuous measurements were limited to that period.

In practice, the oximeter earpiece is attached to the patient's ear firmly to prevent spontaneous slippage. The light source is turned on for fifteen minutes to allow thermal equilibrium to occur before readings are begun. Since the oximeter does not allow one to determine the absolute value but only changes in

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3. (a) Brown, J. R., and Baker, A. B.: Poliomyelitis: I. Bulbar Poliomyelitis; Neurophysiological Interpretation of the Clinico-Pathological Findings, *J. Nerv. & Ment. Dis.*, to be published. (b) Brown, J. R.; Baker, A. B.; Adams, J., and McQuarrie, I.: The Bulbar Form of Poliomyelitis: I. Diagnosis and the Correlation of Clinical with Physiologic and Pathologic Manifestations, *J. A. M. A.* **134**: 757-762 (June 28) 1947. (c) Priest, R. E.; Boies, L. R., and Goltz, M. F.: Tracheotomy in Bulbar Poliomyelitis, *Ann. Otol., Rhin. & Laryng.* **56**:250, 1947. (d) Kubicek, W. G.; Holt, G. W.; Elam, J. O.; Brown, J. R., and Gullickson, G.: Oxygen Therapy in Poliomyelitis: A Tracheotomy Inhalator, *Arch. Phys. Med.* **29**:217, 1948.

4. (a) Millikan, G. A.: The Oximeter, an Instrument for Measuring Continuously the Oxygen Saturation of the Arterial Blood in Man, *Rev. Scient. Instruments* **13**:434, 1942. (b) Smaller, B.: Report EXP-M-54-653-102 United States War Department, May 4, 1942; Report EXP-M-49-696-16, *ibid.*, Aug. 28, 1942. (c) Hemingway, A., and Taylor, C. B.: Laboratory Tests of the Oximeter with Automatic Compensation for Vasomotor Changes, *J. Lab. & Clin. Med.* **29**:987, 1944. (d) Liston, M. D.; Quinn, C. E.; Sargeant, W. E., and Scott, G. G.: A Contact Modulated Amplifier to Replace Sensitive Suspension Galvanometers, *Rev. Scient. Instruments* **17**:194, 1946. (e) Hemingway, A.: A Physiologic Investigation of Events Occurring when Changing from Oxygen to Air at 55,000 Feet, *J. Aviation Med.* **15**:685, 1944.

oxygen saturation, it is necessary to know the initial value of oxygen saturation if changes are to be assigned absolute values. The initial value of arterial oxygen saturation can be obtained with absolute certainty only by direct measurement. In these studies it was frequently determined by the Van Slyke<sup>6</sup> manometric method or the Scholander-Roughton micromethod.<sup>7</sup> However, for most practical purposes it is fortunately unnecessary to make these time-consuming chemical measurements. It is more practical to assume tentatively that the arterial blood is fully saturated after prolonged breathing of 100 per cent oxygen when the minute respiratory volume is normal. This assumption is obviously invalid in severe alveolar deficiency (and in the presence of anomalies of the great vessels), but no false deductions ordinarily result from this error. Consequently in these studies the oximeter recorder was usually set at 100 per cent when the patient was adequately ventilated with 100 per cent oxygen for ten minutes. In few instances did the chemically measured oxygen saturation differ from the assumed value by more than 2 per cent.

## OBSERVATIONS

### I. SPINAL INVOLVEMENT

CASE 1.—*Severe Ventilatory Deficiency in Spinal Poliomyelitis*.—M. P., a 24 year old white woman, was admitted to University Hospitals on Aug. 3, 1946, after the onset of paralysis of the intercostal muscles. Paralysis of the diaphragm and of the lower extremities occurred on August 8. The patient was placed in a respirator.

By August 22 there had been no clinical improvement. The patient had remained in the respirator constantly. A function test for ventilatory deficiency indicated severe impairment (fig. 1A). Opening of the respirator ports to render the respirator pressure ineffective and allow the patient to attempt ventilation independently was followed by a precipitous decrease in saturation, which was promptly restored to 90 per cent when the ports were closed. The remainder of the test represents evaluation of treatment. Obviously the repeated opening of the respirator ports, which was necessary for routine care, was inflicting multiple episodes of anoxia. Accordingly the protection afforded by the administration of oxygen when the ports were open was determined. When oxygen was given at the instant the ports were closed the saturation quickly returned to 95 per cent. However, if oxygen was administered at the time the ports were opened the saturation decreased

5. It was found that electrical artefacts which appeared on the tracing as rapid irregular excursions of the recorder pen could be entirely eliminated by suitable grounding of the high gain amplifier being used. The formation of local edema at the site of the oximeter earpiece caused another artefact consisting of a gradual downward drift in the recorded value in tests of several hours' duration. To determine the presence and the magnitude of this artefact, the conditions of the previously recorded reference saturation were duplicated and the resulting saturation compared with the reference value. Unfortunately the only available earpiece, an adult size, excluded the use of oximetry for patients with small ears.

6. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

7. Scholander, P. F., and Roughton, F. J. W.: *Micro Gasometric Estimation of the Blood Gases: I. Oxygen*, J. Biol. Chem. **148**:541, 1943.



only 5 per cent within eight minutes, whereas without oxygen the saturation had decreased 15 per cent within one minute.

Pronounced ventilatory deficiency persisted (fig. 1B). It was found that the maximal protection against the hypoxia due to suspension of the artificial respiration was attained by giving oxygen for five minutes before the ports were opened as well as while they were opened. In this way the patient achieved full saturation before ventilation was essentially stopped. Under these conditions the patient could tolerate suspended ventilation for a period of eight minutes, with the arterial oxygen saturation remaining about 98 per cent. At the end of eight minutes she experienced mild dizziness which was associated with hypercapnia.

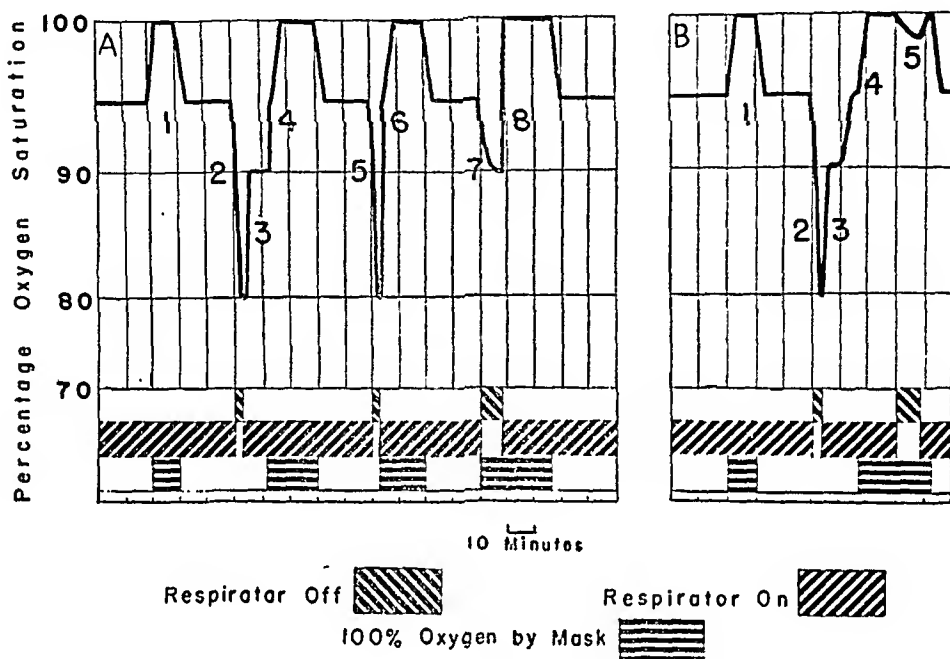


Fig. 1.—Function tests in a patient in a respirator with paralysis of the diaphragm and the intercostal muscles. Reference saturation in both tests at 95 per cent with the patient in the respirator and breathing air. The patient had been in the respirator for three weeks (A) and for six weeks (B) when the respective tests were done. Note the rapid onset of hypoxia, a decrease of 15 per cent in the saturation within one minute, when the use of the respirator was momentarily discontinued (2 and 5 in A and 2 in B). The response would have been considerably greater in each instance had not the respirator been started when the saturation reached 80 per cent. This finding is typical of severe ventilatory deficiency. From a comparison of 3 and 6 in A and 3 in B it is apparent that the saturation could be restored to normal more rapidly if oxygen were administered when the respirator was started (or when the ports were closed). However, when oxygen was given at the time the use of the respirator was discontinued (7 in A), the resulting hypoxia was limited to a 5 per cent decrease within eight minutes. In B note that twelve minutes were required for the saturation to return to normal when the respirator alone was used. In the same diagram 5 indicates that the maximal protection against the hypoxia due to the discontinuation of the use of the respirator was obtained when the patient received oxygen before the ports were opened. In this instance the saturation decreased only 2 per cent during the eight minutes the patient was without artificial respiration.

CASE 2.—Mild Ventilatory Deficiency in Spinal Poliomyelitis.—E. K., a 17 year old white girl, experienced onset of weakness of the diaphragm and of the inter-

costal muscles on Aug. 10, 1946, the third day of illness. She was admitted to University Hospitals and placed in a respirator.

On August 11 she was given a trial out of the respirator under clinical observation. Fatigue developed after four minutes. By September 6 the periods out of the respirator had been gradually increased on the basis of clinical impression until the patient was being allowed to breathe independently for sixty-four minutes daily. A function study was started at the end of this sixty-four minute period to determine objectively whether she could tolerate additional time out of the respirator without suffering hypoxia. It was found that she was able to maintain a normal arterial oxygen saturation for four hours and fifty-nine minutes without

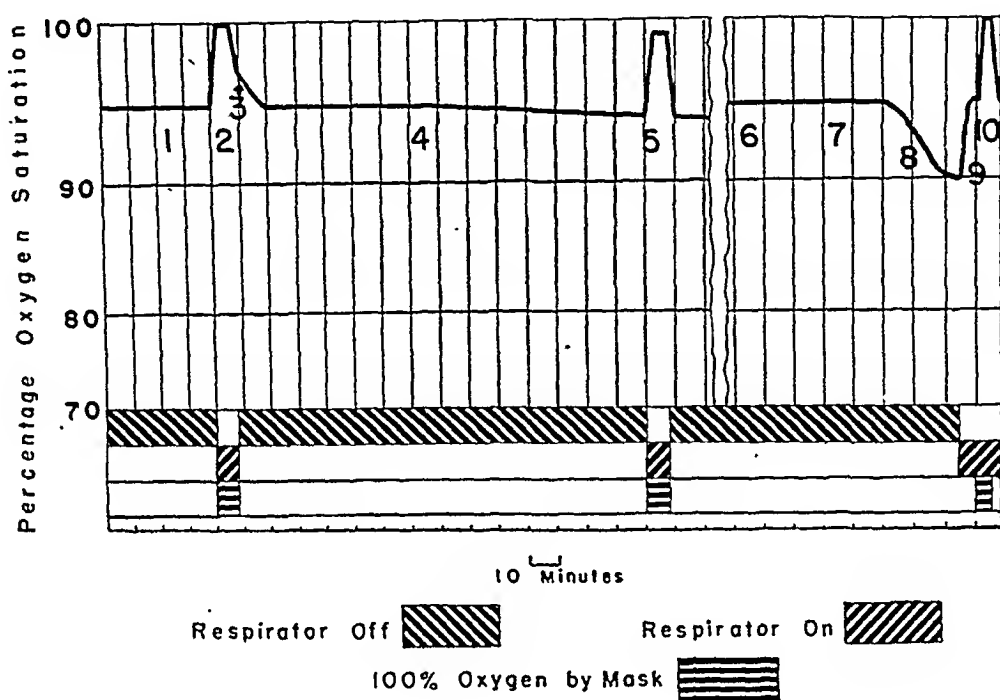


Fig. 2.—Function test in a patient in a respirator with incomplete paralysis of the diaphragm and the intercostal muscles. Reference saturation at 95 per cent with the patient out of the respirator and breathing air. When this test was carried out the patient had been in the respirator for four weeks because of weakness of the diaphragm and of the intercostal muscles. She had been out of the respirator for sixty-four minutes when the test was started. No significant change in the recorded saturation occurred until she had been out of the respirator for four hours and fifty-nine minutes, when a decrease of 5 per cent was recorded (8). This finding indicated a mild ventilatory deficiency. When the respirator was started the saturation returned to 95 per cent (9), and the administration of 100 per cent oxygen gave a normal saturation response of 100 per cent. Chemical analysis of arterial blood showed an oxygen saturation of 97 per cent (3). For calibration, 100 per cent oxygen was given for a brief period while the respirator was turned on (2, 5, and 10).

artificial respiration (fig. 2). At the end of this period the saturation decreased gradually from 95 to 90 per cent and remained stabilized until the respirator was started. She experienced no distress or fatigue at this time. Accordingly she was started on a schedule of three hours out of the respirator daily, with frequent increases in this period on the basis of repeated ventilatory function tests. By September 27 the patient was able to be out of the respirator without suffering hypoxia for fourteen hours daily. On October 5 the use of the respirator was discontinued.

## II. BULBAR INVOLVEMENT

CASE 3.—*Alveolar Deficiency in Acute Bulbar Poliomyelitis*.—D. T., a 13 year old white boy, was admitted to University Hospitals on Aug. 17, 1946, with the history of acute bulbar symptoms for three days. Tracheotomy was performed on admission, and the use of 50 per cent oxygen by tracheotomy inhalator<sup>3d</sup> was started.

On August 23 intermittent apnea developed and the patient was placed in a respirator. A function study was started two hours later. At this time the apnea

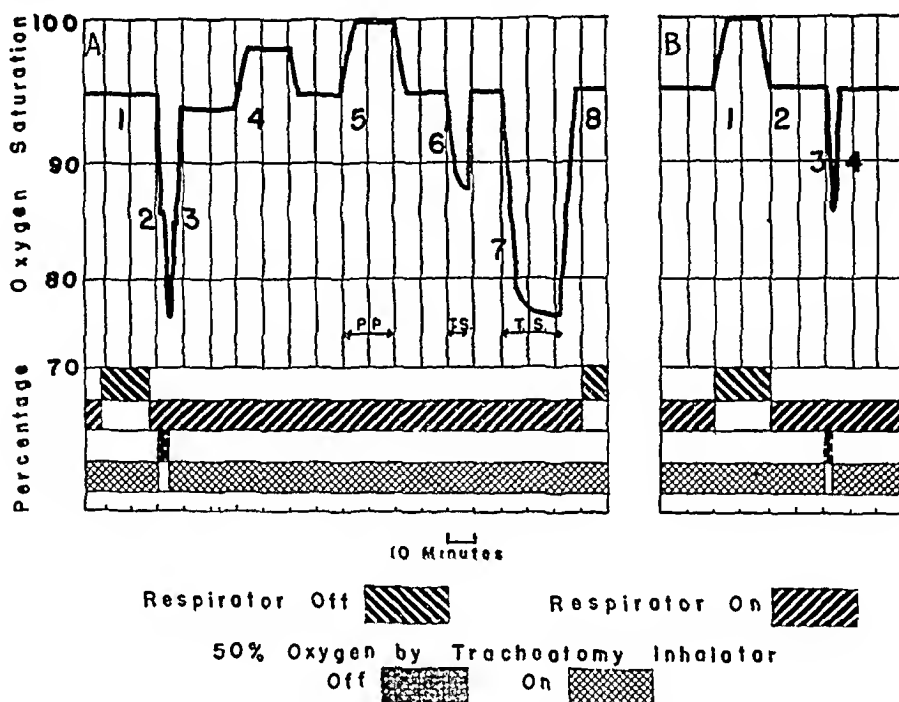


Fig. 3.—Function tests in a patient who had undergone tracheotomy and who required the respirator because of apnea. Reference saturation at 95 per cent with the patient in a respirator and breathing 50 per cent oxygen by tracheotomy inhalator. The symbols P P indicate positive pressure during expiration; T. S. refers to tracheotomy tube suction. The patient had severe bulbar involvement for five days before the first test (A) was done. Treatment had consisted of tracheotomy, administration of 50 per cent oxygen by tracheotomy inhalator and the use of the respirator for control of apnea. Since no changes occurred in the saturation when the respirator was discontinued (1 and 8 in A), no ventilatory deficiency is demonstrated. However, when air was substituted for the 50 per cent tracheal oxygen, severe hypoxia developed rapidly (2 in A). The use of positive pressure of 3 cm. of water during expiration was found to increase the saturation either when the nose was occluded (4 in A) or when 100 per cent oxygen was given by mask (5). Suction of the tracheotomy tube (6 and 7) produced hypoxia, which in one instance was extended over a period of twenty-eight minutes. This test indicated alveolar deficiency. The second test (B) was carried out three days later and showed an actual increase in saturation when the use of the respirator was discontinued (1 in B). It was noted that the patient's own respiratory rate was 32 per minute and the respirator was being operated at 18 cycles per minute. Substituting air for 50 per cent tracheal oxygen (3 in B) revealed persisting alveolar deficiency.

apparently had been successfully controlled. No changes occurred in the arterial oxygen saturation when the patient was allowed to breathe independently (fig. 3A). No ventilatory deficiency was demonstrated. However, when the patient breathed air instead of the 50 per cent oxygen there was a rapid onset of hypoxia, which

indicated a definite alveolar deficiency. During the rest of this test the patient's reaction was evaluated. When 50 per cent oxygen was administered by tracheotomy inhalator with a positive pressure of 3 cm. of water during expiration there was a 3 per cent increase in saturation. In order to render this pressure effective it was necessary to occlude the nose (see 4 in figure 3A). When this pressure was used during the administration of 100 per cent oxygen by mask, the saturation increased 5 per cent. The routine tracheotomy tube suction which had been ordered every fifteen minutes for the removal of accumulated secretions resulted in considerable hypoxia. In one instance the hypoxia due to tracheotomy tube suction was extended over a period of twenty-eight minutes.

By August 27 the patient had improved. He had been left in the respirator because of the risk that apnea might recur. However, the return of function of the respiratory center resulted in an asynchronism between the patient's respiratory rate of 32 per minute and the 18 cycles per minute of the respirator. During another function study (fig. 3B), it was found that the patient actually increased his arterial oxygen saturation by 5 per cent when the respirator was turned off. A trial without 50 per cent oxygen by tracheotomy inhalator again indicated alveolar deficiency. For this reason oxygen therapy was continued. The use of the respirator was discontinued and was not required further during his course in the hospital.

By September 9 he was able to maintain a normal oxygen saturation while breathing air, which indicated that there was no further need for oxygen therapy. Oximetry was employed subsequently as a basis for removal of the tracheotomy tube.

*CASE 4.—Severe Alveolar Deficiency in Acute Bulbar Poliomyelitis.*—C. S. U., a 22 year old white man, was admitted to the hospital on Aug. 25, 1946, the seventh day of acute bulbar symptoms. There was a history of dysphagia, regurgitation of fluid through the nose, choking and difficulty in speech of two days' duration. Tracheotomy was performed immediately, and the use of 50 per cent oxygen by tracheotomy inhalator was started.

On August 25 cyanosis suddenly developed when the flow of oxygen through the inhalator was momentarily interrupted. During this brief interval, he was breathing ambient air. Frothy pink fluid drained from the nose, the mouth and the tracheotomy tube. Loud gurgling rales were grossly audible. Suction of the tracheotomy tube yielded 75 cc. of edema fluid. Administration of oxygen by positive pressure was started immediately. A pressure of 12 cm. of water was applied during inspiration by manual compression of the rubber breathing reservoir bag (similar to the technic commonly used in anesthesia). An expiratory positive pressure of 12 cm. of water was also used in the inhalator. One hundred per cent oxygen was given concomitantly by mask.<sup>3d</sup> The patient's color promptly returned to normal, and after thirty minutes of this therapy no rales could be detected over the pulmonary fields. It was found that when oxygen therapy was discontinued and the patient allowed to breathe air the arterial oxygen saturation decreased more than 15 per cent rapidly (fig. 4). This finding established the presence of alveolar deficiency since there was no evidence that ventilation was impaired. The additional data were for the purpose of evaluating treatment. When 50 per cent oxygen was given via inhalator with a positive expiratory pressure of 4 cm. of water but without occlusion of the nose, a saturation of 95 per cent was recorded. Occlusion of the nose resulted in a gradual increase in the saturation to 98 per cent, and this value was not further increased by the use of 100 per cent oxygen by mask (in addition to the 50 per cent oxygen by

tracheotomy inhalator). If these same concentrations of oxygen were continued by trachea and by mask without any positive pressure, the saturation decreased to 90 per cent. On this basis it was decided to continue the administration of 100 per cent oxygen by mask and of 50 per cent oxygen by tracheotomy inhalator with a positive pressure of 4 cm. of water during expiration. In order to protect the patient against fatigue resulting from the expiratory resistance, a pressure

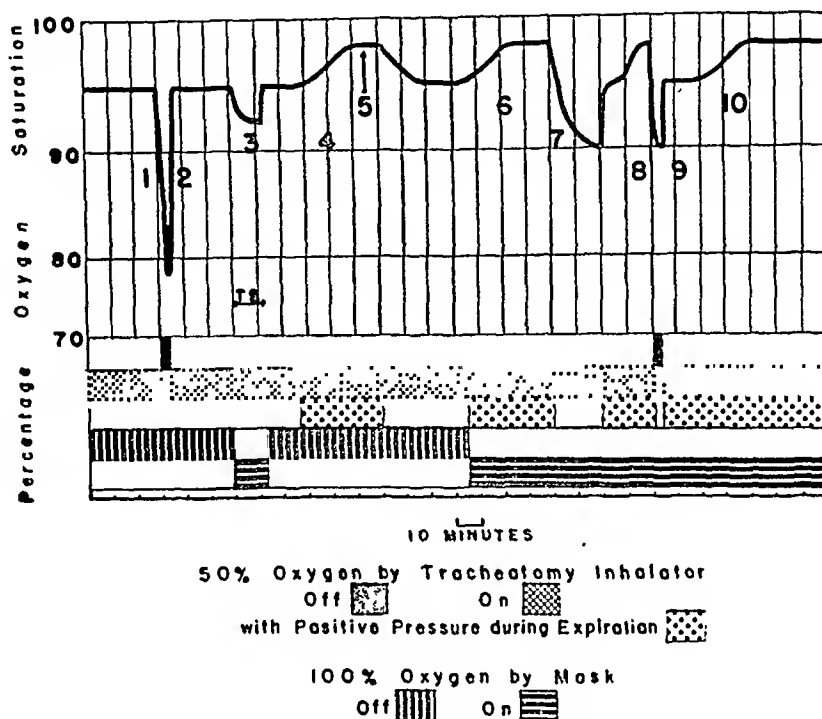


Fig. 4.—Function test in patient who had undergone tracheotomy after recovery from acute pulmonary edema. Reference saturation at 95 per cent with the patient breathing 50 per cent oxygen by tracheotomy inhalator with a positive pressure of 4 cm. of water during expiration (nose not occluded). The patient had been acutely ill for twelve days when this test was done. Treatment had consisted of tracheotomy and of administration of 50 per cent oxygen by inhalator. Positive pressures of 12 cm. of water during inspiration and expiration had been used for thirty minutes just prior to the test in order to reverse the pulmonary edema. Note the rapid onset of hypoxia when oxygen therapy was discontinued and the patient allowed to breathe air without resistance (1). This reveals the presence of alveolar deficiency. In evaluation of treatment, it was found that the hypoxia resulting from suction of the tracheotomy tube could be essentially eliminated by the administration of 100 per cent oxygen by mask and by continuing the flow of oxygen through the inhalator during this time (3).<sup>3d</sup> The symbols T. S. indicate the period during which suction was applied to the tracheotomy tube. The use of positive pressure during expiration resulted in an increase of the saturation from 95 to 98 per cent either when the nose was occluded (4) to render the pressure effective or when 100 per cent oxygen was given by mask (6). Arterial blood was found by chemical analysis to have an oxygen saturation of 98.1 per cent (5). When the same concentrations of oxygen were continued through mask and inhalator without positive pressure the saturation decreased 8 per cent (1). The difference between 3 and 8 indicates the advantage of continuing the flow of oxygen through the inhalator when suction of the tracheotomy tube is required. In 8 the tracheotomy inhalator was detached, so that the patient breathed air through the tracheotomy opening, but the use of 100 per cent oxygen by mask was continued. Note the prolonged saturation responses (4, 6 and 10).

vest was used intermittently. This method of artificial respiration produces active expiration and passive inspiration. The pressure vest is similar in principle to the Bragg-Paul pulsator commonly used in England.

**CASE 5.—Prolonged Alveolar Deficiency in Convalescent Bulbar Poliomyelitis.**—E. M., a 25 year old white man, was admitted to the hospital on Aug. 19, 1946, with a partial laryngeal obstruction. Tracheotomy was performed immediately.

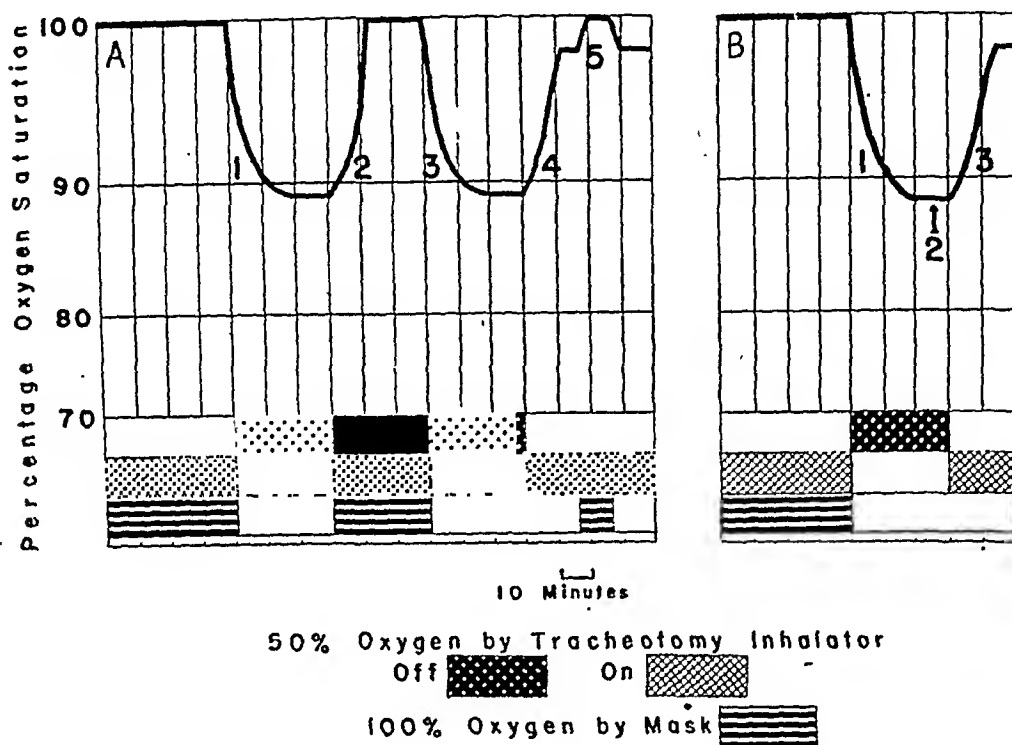


Fig. 5.—Function tests in a patient who had undergone tracheotomy on the thirteenth and twenty-fifth days in the hospital. Reference saturation at 100 per cent with patient breathing 100 per cent oxygen by mask and 50 per cent oxygen by tracheotomy inhalator. On both occasions the patient suffered a mild hypoxia when allowed to breathe air (1 and 3 in A and 1 in B). Note that the saturation responses as well as the saturation times were increased, which indicated a persisting alveolar deficiency. An arterial sample was found by chemical analysis to have a saturation of 89.7 per cent (2 in A). Under the conditions of treatment a saturation of 98 per cent was being maintained by the use of 50 per cent oxygen in the tracheotomy inhalator (after 5 in A and 3 in B).

Administration of 50 per cent oxygen by tracheotomy inhalator was started. He was acutely ill, with periods of coma, delirium and disorientation.

By August 26 the acute phase of bulbar involvement had apparently subsided and the patient showed much improvement. He had remained free of ventilatory impairment. The question of how long oxygen therapy should be continued was studied by means of repeated function tests. At this time it was found that the arterial oxygen saturation was 89 per cent when the patient breathed air, which indicated a mild alveolar deficiency (fig. 5A). The patient noticed no distress during this period of hypoxia. A saturation of 98 per cent was being maintained by the use of 50 per cent oxygen in the tracheotomy inhalator.

After twenty-five days in the hospital the patient still required oxygen therapy, as shown by a repeated function test (fig. 5B). The hypoxia which accompanied the substitution of air for the 50 per cent oxygen by tracheotomy inhalator was

essentially the same as that previously recorded. On the thirty-ninth day the patient demonstrated a normal arterial saturation while breathing air. Accordingly oxygen therapy was discontinued.

CASE 6.—*Adequate Ventilatory and Alveolar Function in Convalescent Bulbar Poliomyelitis.*—A. P., a 31 year old white man, was admitted to the hospital on Oct. 2, 1946, the ninth day of his acute illness. On October 3 difficulty in swallow-

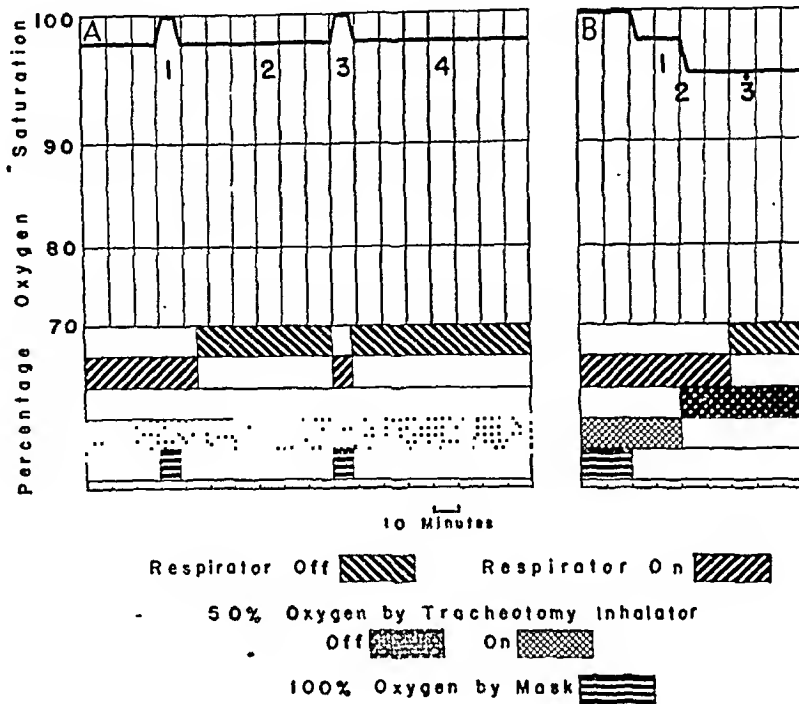


Fig. 6.—Function tests in a patient who had undergone tracheotomy and who required artificial respiration for control of apnea. Reference saturation at 98 per cent with patient in respirator and breathing 50 per cent oxygen by tracheotomy inhalator. These tests were carried out on the fourteenth and sixteenth days of illness. Treatment had consisted of tracheotomy and of administration of 50 per cent oxygen by tracheotomy inhalator. The first test (A) demonstrated the absence of ventilatory deficiency since the saturation remained constant when the respirator was discontinued (2 and 4). This finding was confirmed in the second test (B), in which it was also shown that the patient had no alveolar deficiency. When oxygen therapy was discontinued the saturation decreased to the normal 95 per cent (2). Arterial blood showed an oxygen saturation of 96.5 per cent as determined by chemical analysis (3 in B). Note that the saturation time as well as the saturation response is within normal limits.

ing, mild cyanosis and anoxic euphoria occurred. Tracheotomy was performed, and administration of 50 per cent oxygen by tracheotomy inhalator was started, a positive pressure of 3 cm. of water being employed during expiration. A function test at this time for evaluation of treatment indicated that a normal saturation was being maintained.

On September 4 irregular diaphragmatic excursions developed, which suggested depression of the respiratory center. The patient was placed in a respirator. A function test on September 7 showed no ventilatory deficiency (fig. 6A) since there was recorded no change in the arterial oxygen saturation when the use of the respirator was discontinued. However, because of the risk of fatigue or of

recurrence of apnea the patient was left in the respirator. On September 9 a function test indicated a normal saturation when the use of both the respirator and oxygen therapy was discontinued; this indicated the absence of both ventilatory and alveolar deficiency (fig. 6B).

### III. BULBOSPINAL INVOLVEMENT

CASE 7.—*Alveolar Deficiency in Acute Bulbospinal Poliomyelitis.*—F. L. W., a 28 year old white man, experienced the onset of acute spinal symptoms on Sept. 7, 1946. He was admitted to University Hospitals on September 8. No disturbance in respiration existed at this time.

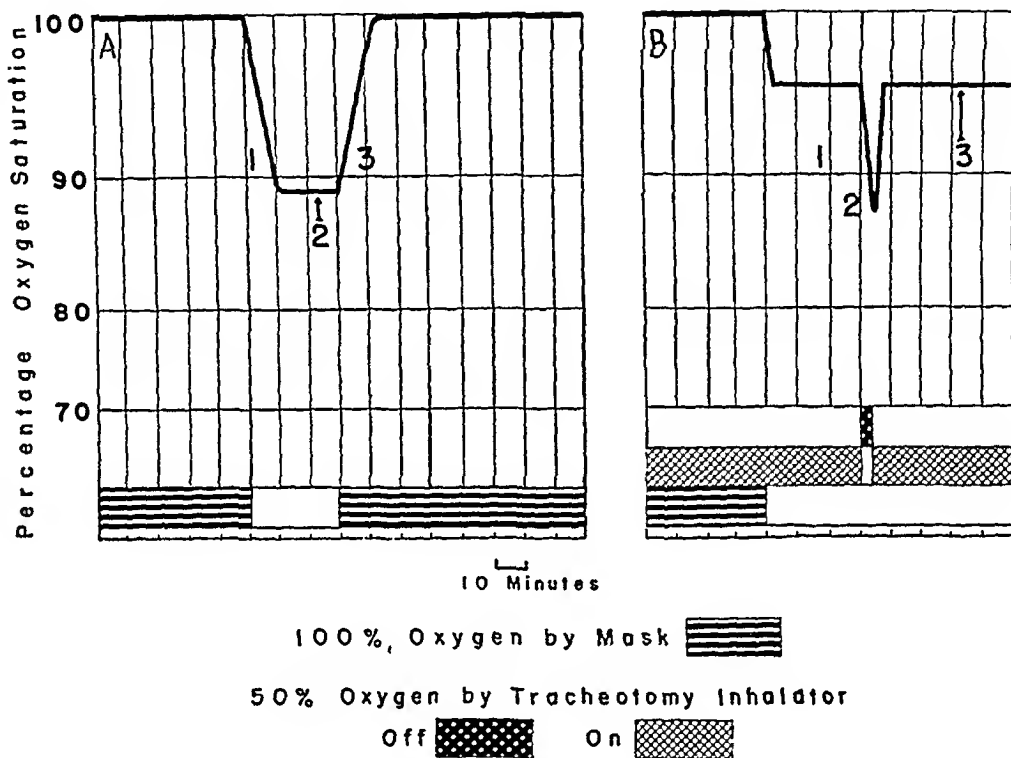


Fig. 7.—Function tests in patients with acute bulbospinal poliomyelitis before and after tracheotomy. Reference saturation at 100 per cent with the patient breathing 100 per cent oxygen by mask for fifty minutes. The first test (A) was carried out twenty-four hours prior to tracheotomy. The second test (B) was done three hours after tracheotomy. Note the hypoxia in (A) and the increase in saturation time when the inspired air was changed from 100 per cent oxygen to air (1). Arterial blood revealed a saturation of 89.5 per cent (2). These findings established a definite alveolar deficiency, since ventilation was not impaired. In the subsequent test it was found that under the conditions of treatment a normal (95 per cent) saturation was being maintained (1 in B). Chemical analysis of arterial blood showed a saturation of 95.3 per cent (3). This test confirmed the presence of alveolar deficiency (2).

On September 15 complete paralysis of all extremities occurred; there was a definite weakness of the intercostal muscles. Ventilation was not impaired, however. On September 17 a mild irritability developed, which suggested hypoxia. There was no cyanosis or dyspnea. A function test was carried out to determine the presence of alveolar deficiency since ventilation was still adequate. It was found that the patient's arterial oxygen saturation was 89 per cent while he breathed air (fig. 7A). The administration of 100 per cent oxygen by mask



increased the recorded value to 100 per cent, but this required twelve minutes. The increase in saturation time and the response indicated a definite alveolar deficiency. On the basis of these findings, oxygen therapy was started, but the patient became irrational and combative. For this reason attempts to give oxygen by mask and later by nasal catheter were unsuccessful.

By September 18 bulbar involvement could be definitely established since difficulty in swallowing and in speech, irregular respiratory rhythm and occasional diaphragmatic flutter developed, which suggested depression of the respiratory

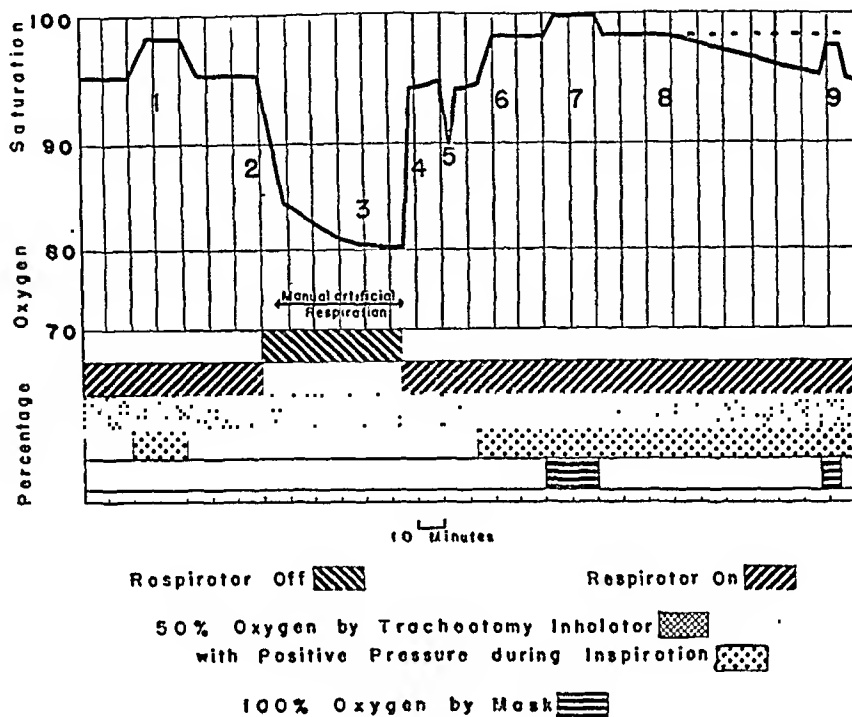


Fig. 8.—Function test in patient with acute bulbar poliomyelitis who had undergone tracheotomy and was in a respirator. Reference saturation at 95 per cent with the patient in respirator and receiving 50 per cent oxygen by tracheotomy inhalator with a positive pressure of 4 cm. of water during expiration. Note that the use of a positive pressure of 8 cm. of water during inspiration increased the saturation to 98 per cent (1). The decrease in saturation seen at 2 was due to discontinuation of the use of the respirator when the rubber neckpiece accidentally slipped loose. Manual artificial respiration was carried out during the forty-five minutes indicated, with the patient remaining in the respirator (3). This finding confirmed the presence of ventilatory deficiency. When oxygen therapy was discontinued for three minutes (5) the saturation fell rapidly but was not allowed to proceed. Thus alveolar deficiency is also demonstrated. The use of positive pressure of 8 cm. of water during inspiration was continued for the remainder of the test. The addition of 100 per cent oxygen by mask increased the saturation only 2 per cent (7). The dotted line indicates the actual saturation value corrected for drift artefact demonstrated to be 2 per cent (9).

center. Tracheotomy was performed, and administration of 50 per cent oxygen by tracheotomy inhalator was started. A function study after tracheotomy indicated that under the conditions of treatment a normal arterial oxygen saturation was being maintained (fig. 7B). Because tracheotomy and effective oxygen therapy had relieved the patient's hypoxia, his alveolar deficiency appeared to

have been associated with a partial laryngeal obstruction which had contributed toward the development of a subacute pulmonary edema.

CASE 8.—*Ventilatory and Alveolar Deficiency in Acute Bulbospinal Poliomyelitis.*—M. B., a 31 year old white man, was admitted to the hospital on Aug. 20, 1946, the third day of acute spinal symptoms. He was placed in a respirator on his admission. On August 21 complete laryngeal obstruction developed, which led immediately to deep cyanosis and extensive pulmonary edema. After laryngeal intubation with a Mosher tube and aspiration of 200 cc. of foamy serous fluid, 100 per cent oxygen was insufflated through the Mosher tube while an emergency tracheotomy was performed. During this time it was observed that the action of the respirator apparently increased the severity of the patient's pulmonary edema, as indicated by the amounts of fluid aspirated from the trachea. For this reason the use of the respirator was discontinued and oxygenation was maintained by oxygen insufflation alone. Slight cyanosis persisted during this time. On completion of the tracheotomy, the respirator was started and 100 per cent oxygen was administered with a positive pressure of 12 cm. of water during inspiration and expiration through the tracheotomy inhalator until the patient's color returned to normal. At this time the inhalator mixture was changed to 50 per cent oxygen, and a function test was made to determine how adequate oxygenation could be maintained. A positive pressure of 4 cm. of water during expiration with 50 per cent oxygen through the inhalator was found to be satisfactory.

The results of a follow-up function test on August 21 for the purpose of evaluating both pulmonary deficiency and treatment are shown in figure 8. It was found that the use of 8 cm. of positive pressure during inspiration increased the saturation 3 per cent. At this juncture an accidental slipping of the rubber neckpiece of the respirator occurred, and the resulting leak rendered the respirator ineffective. A period of fifty-eight minutes was required to reattach the neckpiece. During the first eight minutes of this period the patient's saturation decreased to 84 per cent. A modified Schaeffer method of artificial respiration had been started when the saturation reached 90 per cent. For an interval of forty-eight minutes 18 compressions per minute of the anterior part of the thoracic wall by two operators (each with one hand extended through a respirator port) maintained the saturation above 80 per cent. The patient's saturation returned to normal promptly when the respirator was started. Thus he had pronounced deficiency of ventilatory function. The decrease in saturation that occurred when air was substituted for 50 per cent oxygen by tracheotomy inhalator was not followed below 90 per cent because of the previous inadvertent hypoxia. This response was sufficient to establish the presence of alveolar deficiency, however. During the remainder of the test the positive inspiratory pressure of 8 cm. of water was found to maintain a saturation of 98 per cent when 50 per cent oxygen by tracheotomy inhalator was administered, with the nose occluded. The addition of 100 per cent oxygen by mask increased the saturation to 100 per cent.

#### COMMENT

During the epidemic the aforementioned tests were used repeatedly to study pulmonary function in 43 patients. The recording oximeter has

proved to be a valuable clinical tool for evaluating ventilatory and alveolar deficiency.

The high incidence of hypoxia in patients with acute poliomyelitis of spinal, bulbar and bulbospinal types and in convalescent patients has not received sufficient attention previously. The significance of hypoxia during any stage of this disease is obvious from the viewpoint of effective treatment involving optimal conditions for the survival of viable neurons.<sup>8</sup> The differentiation between ventilatory and alveolar deficiencies in poliomyelitis has therapeutic implications of prime importance. For example, for a patient with alveolar impairment and without ventilatory deficiency in whom there is an inability to absorb adequate oxygen from the air, artificial respiration is ineffective because it merely guarantees an adequate ventilation and does not increase significantly oxygen tension in the alveoli. It should be recognized that neither oxygen therapy nor artificial respiration is successful in the presence of obstruction of the upper airways until patency is reestablished.<sup>9</sup>

The evaluation of pulmonary deficiency need not be limited to clinical impression. Observation of the adequacy of diaphragmatic and thoracic excursions affords only a crude estimation. The ability of the patient to remain free of cyanosis is an unreliable index of adequate oxygenation. Determinations of vital capacity, tidal air volume and respiratory minute volume and various indexes of ventilatory reserve<sup>1</sup> may be employed for the detection of ventilatory deficiency. Alveolar function as well as ventilatory function may be assayed by oximetry or by chemical analysis of the arterial blood for oxygen saturation. Oximetric procedures are advantageous because of their convenience for obtaining results immediately during different conditions and because ventilatory deficiency, alveolar deficiency and treatment may be evaluated during a single procedure. By the routine use of tests similar to those herein reported the causes of repeated hypoxic episodes during the attack of poliomyelitis may be detected and sometimes prevented. Reduced arterial oxygenation may exist in the absence of the classic signs and symptoms of anoxia. Changes in oxygen saturation recorded from the ear are presumably paralleled by changes in other blood vessels, including those of the nervous system. The instantaneous record of the

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8. Wright, E. B.: Comparative Study of Effects of Oxygen Lack on Peripheral Nerve, *Am. J. Physiol.* **147**:78, 1946. Heinbecker, P.: Effect of Anoxemia, Carbon Dioxide and Lactic Acid on Electrical Phenomena of Myelinated Fibers of the Peripheral Nervous System, *ibid.* **89**:58, 1929. Gerard, R. W.: The Response of Nerve to Oxygen Lack, *ibid.* **92**:498, 1930. Schmitt, F. O.: On the Oxidative Nature of the Nerve Impulse, *ibid.* **95**:650, 1930.

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changes in arterial oxygen saturation detects the presence of hypoxia before the patient is subjected to fatigue, dyspnea or other undesirable symptoms. In none of the tests conducted was the duration of hypoxia resulting from the test procedures prolonged to the point of onset of cyanosis. Both the duration and the degree of hypoxia may be arbitrarily limited as desired. Obviously oximetry cannot be applied accurately in the evaluation of pulmonary function in the presence of grossly impaired cardiocirculatory function or in the presence of an abnormal oxygen-carrying capacity of hemoglobin, such as occurs in anemia. The tests described are not intended to provide an index of pulmonary reserve function but are useful for detecting deficiency under resting conditions.

The following procedures are recommended for tests of pulmonary function in patients with poliomyelitis and for determining the requirements of oxygen therapy and respirator treatment. One hundred per cent oxygen is administered by mask for ten minutes to a patient before he is placed in a respirator. The oximeter is set at 100 per cent. Administration of oxygen is prolonged for some minutes while recording is continued. If the saturation does not change, the mask is removed and the patient allowed to breathe room air. The saturation falls both in normal subjects and in patients with poliomyelitis when this maneuver is carried out. However, if the fall is greater than 8 per cent, it is presumed that there is abnormality. If the fall is greater than this, the patient is placed in a respirator and 100 per cent oxygen is administered again. The fall which occurs when a change to room air is made is studied again at several levels of ventilation. If the fall in saturation with normal or supernormal values of respiratory minute volume (with the change from 100 per cent oxygen to air) is 8 per cent or less, the patient was probably suffering from simple ventilatory deficiency while out of the respirator. If the decline in saturation with the foregoing maneuver is greater than 8 per cent, the patient is probably in a state of alveolar deficiency, the degree being proportional to the magnitude of the fall. Since arterial oxygen saturations below 80 per cent are potentially deleterious, even for short periods, the value is not allowed to fall below that level.

The presence of combined ventilatory and alveolar deficiency can be detected by determining whether the patient suffers a decline in oxygen saturation of more than 8 per cent on changing from 100 per cent oxygen to room air and also whether there is a fall when artificial respiration is stopped. For a practical test, one can determine first the fall in oxygen saturation when a change is made from oxygen to room air with the patient in the respirator. If it is greater than 8 per cent, the oxygen percentage in the inspired air can be increased gradually until the saturation is 92 per cent. Then the use of the respirator can be stopped and

a change in saturation noted. A requirement of more than 20 per cent oxygen and a fall in saturation under the foregoing conditions establishes combined alveolar and ventilatory deficiency.

The ability of patients to tolerate removal from the respirator is tested by establishing first the oxygen saturation while the patient is breathing room air. The saturation is then recorded continuously while the use of the respirator is discontinued. The respiratory efforts and the saturation record are both observed continuously, and the respirator is restarted when the saturation has fallen to 85 per cent. This test, without danger to the patient, distinguishes between the apprehensive patient who can actually tolerate long periods without the respirator and the patient with severe, true ventilatory deficiency. It also permits the physician to reassure the apprehensive patient, with the fortification of an objective measure of respiratory efficiency to guide his treatment.

Certain suggestions with respect to the treatment of patients with poliomyelitis who have disturbances in respiration are evident from the findings obtained in this series of function tests.

#### SUMMARY

Oximetric procedures to detect ventilatory deficiency, alveolar deficiency and the adequacy of treatment have been described. The findings in 8 patients with poliomyelitis of the spinal, bulbar and bulbospinal types have been presented.

These findings suggest the following conclusions regarding treatment:

1. Patients with severe ventilatory deficiency in respirators suffer hypoxia rapidly when the respirator ports are opened. This may be delayed by administration of 100 per cent oxygen by mask for a period of five minutes before the ports are opened until they are closed.
2. Oximetry provides a basis for safely liberating a convalescent patient from the respirator. The distinction between apprehensiveness on the part of the patient and genuine ventilatory deficiency can be made with assurance. The maximum safe limit of time for release from the respirator can be measured.
3. When the patient in a respirator is unable to synchronize his respiratory rate and rhythm with that of the respirator, the result may interfere with effective ventilation.
4. Patients with respiratory impairment of undemonstrable cause may be found on oximetric study to have hypoxia in the absence of frank clinical signs or symptoms. One such patient reported on showed a decreased arterial oxygen saturation twenty-four hours before a definite laryngeal obstruction was diagnosed. Tracheotomy and effective oxygen therapy relieved the hypoxia

for which oxygen by mask and nasal oxygen therapy had been unsuccessful.

5. Routine tracheotomy tube suction for removal of accumulated secretions may produce severe hypoxia. In some cases this has been minimized by giving 100 per cent oxygen by mask and continuing the flow of oxygen through the tracheotomy inhalator during the interval of the suction procedure.
6. A modified method of the Schaeffer type of artificial respiration used for a patient remaining in the respirator was found to sustain an arterial oxygen saturation 15 per cent below that afforded by the respirator.
7. A small fraction of patients convalescent from poliomyelitis required oxygen therapy for as long as six weeks. Clinical indications of lack of oxygen were absent when the patients breathed air although a definite hypoxia was demonstrated by oximetry.
8. Increase of the pulse rate occurred with mild hypoxia and was a useful clinical indication for oxygen therapy.

Drs. A. B. Baker and Irvine McQuarrie, of the Minnesota Poliomyelitis Research Commission, and Drs. H. S. Wells, W. G. Kubicek, G. W. Holt, E. B. Brown and A. H. Sussman cooperated and assisted in this work. Miss Mary Lou Smersh gave technical assistance. Apparatus was loaned to the University of Minnesota by the American Air Force School of Aviation Medicine, Randolph Field, the Aeromedical Laboratory at Wright Field, the Aeromedical Laboratory of the Mayo Foundation and the Perkin-Elmer Corporation, Glenbrook, Conn. Cooperation in obtaining equipment by rapid delivery during the epidemic was furnished by the Coleman Instrument Company, Maywood, Ill., General Motors Laboratory, Detroit, and the Leeds and Northrup Co., Philadelphia.

## CIRRHOSIS FOLLOWING INFECTIOUS HEPATITIS

A Report of Five Cases, in Two of Which There Was Superimposed Primary Liver Cell Carcinoma

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AND

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IN AN APPRECIABLE number of cases infectious hepatitis leaves clinical evidence of impaired hepatic function and in some instances manifests itself as a chronic, probably progressive, disease. We believe that in some cases the morphologic pattern of its late stages is distinct, although its clinical course is indistinguishable from that of Laennec's cirrhosis or acute hepatic failure.

In this report we present 5 cases in which cirrhosis, we believe, resulted from infectious hepatitis. Primary liver cell carcinoma developed in 2 of these. In 4 the cirrhosis was clinically indistinguishable from Laennec's cirrhosis; the morphologic findings ruled out this diagnosis, and the fundamental lesion of the liver was identical with that described by F. B. Mallory as "toxic cirrhosis." Our few cases, however, do not preclude types of lesions other than that reported here as end results of infectious hepatitis.

Observations concerning the outcome of infectious hepatitis have resulted in two opposed patterns of thought. Lucké<sup>1</sup> has concluded on the basis of his observations that complete restoration of hepatic parenchyma occurs in nonfatal cases of the disease. On the other hand, the literature contains many demonstrations that the functional integrity of the liver is not restored after a bout of hepatitis. Kornberg,<sup>2</sup> Soffer

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1. Lucké, B.: The Structure of the Liver After Recovery from Epidemic Hepatitis, *Am. J. Path.* **20**:595-620 (May) 1944.

2. Kornberg, A.: Latent Liver Disease in Persons Recovered from Catarrhal Jaundice and in Otherwise Normal Medical Students as Revealed by the Bilirubin Excretion Test, *J. Clin. Investigation* **21**:299-308 (May) 1942.

and Paulson<sup>3</sup> and Altschule and Gilligan,<sup>4</sup> as well as many others, have emphasized the functional impairment that persists for a long time after infectious hepatitis, without symptomatic or obvious clinical evidence of hepatic disease. Pratt and Stengel<sup>5</sup> and Bloomfield,<sup>6</sup> as well as many authors writing since the recent outbreaks (Barker and associates<sup>7</sup>; Fox and associates<sup>8</sup>; Klatskin and Rappaport<sup>9</sup>; Neefe<sup>10</sup>; Kelsall and associates<sup>11</sup>), have emphasized the obviously chronic nature of hepatitis in some cases, correlating it with clinical and laboratory evidence of hepatic dysfunction.

This concept that infectious hepatitis may produce permanent residual injury of the liver is further supported by a number of morphologic observations. Some Scandinavian authors (Roholm and Iversen<sup>12</sup>; Krarup and Roholm<sup>13</sup>) have expressed the belief that their liver biopsy specimens had shown a gradual transition from acute hepatitis to fully developed Laennec's cirrhosis. Dible and co-workers<sup>14</sup> concluded that "classical cirrhosis" may follow prolonged infectious hepatitis. Neefe<sup>10</sup> noted a mild, persistent inflammatory process in 2 specimens of liver taken six and nine months after the onset of induced viral hepatitis. He

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did not mention fibrosis. Watson and Hoffbauer<sup>15</sup> have presented cases intended to show the transition from hepatitis to a type of cirrhosis which they considered similar to the so-called hypertrophic biliary cirrhosis of Hanot and for which they suggested the term "cholangiolitic cirrhosis." Fearnley<sup>16</sup> reported a case in which nodular hyperplasia of the liver clinically resembling portal cirrhosis followed infective hepatitis. Droller<sup>17</sup> mentioned 3 cases of cirrhosis subsequent to hepatitis. Steigmann and Popper<sup>18</sup> published 2 cases of hepatitis with protracted biliary obstruction in which autopsy showed cirrhosis. Axenfeld and Brass<sup>19</sup> concluded that in some instances of infectious hepatitis a transition leading to cirrhosis is observed. Klatskin and Rappaport<sup>9</sup> indicated that infectious hepatitis occasionally leads to "nodular cirrhosis" but rarely, if ever, to portal cirrhosis. T. B. Mallory<sup>20</sup> stated that he saw a number of cases of hepatitis in civilians followed by "toxic cirrhosis" as defined by F. B. Mallory.

Thus it is evident that infectious hepatitis in some cases leads to chronic injury of the liver. Two main questions arise from this conclusion: (1) What type of injury results? (2) Does the lesion represent a new entity or does it correspond to other forms of chronic hepatic injury?

#### REPORT OF CASES

CASE 1.—A 22 year old Negro woman was admitted to the hospital during the night of Sept. 8, 1946, and died early the next morning. She had had symptoms of a duodenal ulcer (roentgenographically demonstrated) for seven years. In 1941 she experienced hematemesis and melena, for which she was treated by transfusion. Eight months later she began to complain of weakness and easy fatigability and was found to be jaundiced and to have hyperproteinemia (10.7 Gm. per hundred cubic centimeters) and hyperglobulinemia. Reaction to the Frei test was negative. She had anemia (normochromic erythrocytes). Ability to excrete sulfobromophthalein sodium and hippuric acid was greatly impaired. After a few weeks the jaundice subsided, but the results of liver function tests remained abnormal. She

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was discharged with a diagnosis of questionable subacute yellow atrophy; cirrhosis, however, was being considered. She was readmitted in March 1943. At that time she was again jaundiced; the liver was slightly enlarged, with a firm, smooth, nontender edge. The level of the total serum proteins was normal, but the globulin was slightly increased. The cephalin-cholesterol flocculation test showed a 4 plus reaction. There was impaired excretion of hippuric acid. The gallbladder was normal. Her diet had been good, and there was no evidence of alcoholism. She had remained asymptomatic until two days before the last admission, when epigastric pain began, and she passed five tarry stools. She became nauseated, vomiting clear yellow fluid, only the last of which was blood tinged. The next day she became comatose and was admitted to the hospital.

She was a well developed young Negress, in a semicomatose state. Her skin was warm and only slightly moist. The eyeballs were slightly jaundiced. The lungs were clear, and the heart, except for tachycardia (120 to 150 beats per minute), was normal. The blood pressure was 130 systolic and 60 diastolic. No abdominal tenderness could be elicited, nor could organs be felt. The liver dullness was 6 cm. in extent in the right midclavicular line. Rectal examination revealed feces of a tarry appearance, and a guaiac test indicated presence of blood.

The urine was normal, except for mild pyuria, with a specific gravity of 1.008, but tests for bile and urobilinogen were not made. There were 2,900,000 red cells per cubic millimeter of blood, with 7.1 Gm. of hemoglobin per hundred cubic centimeters of blood: there were 18,000 leukocytes per cubic millimeter, with a normal differential count. The blood nonprotein nitrogen was 51 mg. per hundred cubic centimeters. The spinal fluid was normal.

The coma deepened, and the patient died twelve hours after admission. No hemodilution had occurred, and it was thought that her gastrointestinal bleeding had stopped or at least diminished greatly.

*Autopsy.*—Gross Examination: The scleras were slightly icteric. No ascites was present. The liver weighed 900 Gm. Its surface was diffusely nodular. The nodules ranged from about 2 to 10 mm. in size and were yellowish tan. The intervening tissue was somewhat wrinkled and reddish gray. The consistency of the liver was increased. The cut surfaces showed similar nodules, and the lobular pattern had completely disappeared. The gallbladder and the bile ducts were normal. The spleen weighed 280 Gm. and was of normal consistency. The malpighian corpuscles were indistinct, but the trabeculae were prominent. The esophageal veins were distended, and a small esophageal erosion, 2 by 4 mm., was found near the cardia. The stomach contained about 400 cc. of tarry material that gave a reaction for blood when the guaiac test was applied. Large amounts of similar material were present in the small and large intestines. In the first portion of the duodenum an area of old scarring was seen to involve all layers of the wall. The overlying mucosa appeared thin but intact. Areas of atelectasis were present in the lower lobes of both lungs. The combined weight of the kidneys was 370 Gm., and the organs were not grossly remarkable.

Microscopic Examination: The liver cells formed small and large nodules, which were sometimes confluent. Large areas were completely devoid of liver cells and consisted only of the stroma with bile ducts. The nodules of parenchyma lacked the normal lobular pattern, although the attempt to reproduce the radial distribution of the liver cells around the efferent vein was generally quite obvious.

The intercellular relationship of the liver cells varied. Distinct cords were seen at the periphery, but these were unusually wide and displayed a prominent central cleft. Instead of a parallel arrangement, these cords tended to branch and

anastomose. A definite arrangement of the cells was lacking in the midzonal and central portion.

The liver cells varied somewhat in size, were generally large and occasional ones contained two or three nuclei. Small syncytial masses of cells without distinct cell contours occurred. The cytoplasm was finely granular and rather basophilic. Occasional large nuclei were present, some of which contained a single large vacuole.

Degenerative changes ranging from fatty metamorphosis to necrosis were often observed in the liver cells of the midzonal and central areas. Some liver cells showed hyaline cytoplasmic degeneration. These regressive changes were gradual, and even in necrotic areas the ghostlike outlines of the affected liver cells remained visible. The peripheral zones were rarely involved. Some budding and rare mitotic activity of the peripheral liver cells attested to regeneration.

The bile canaliculi were prominent and often contained small bile plugs.

The sinusoids were, in general, not remarkable. Where degenerative changes occurred in the parenchyma, the Kupffer cells proliferated and phagocytosed cellular debris. Polymorphonuclear leukocytes infiltrated these areas to a variable degree.

The reticulum stroma in the nodules was not remarkable. In the areas devoid of parenchyma the reticulum framework was collapsed and the individual fibers appeared thickened, but there was no evidence of new formation. The reticulum framework in these areas showed the normal arrangement of parallel and cross fibers, thus outlining clearly the collapsed lobules from which the liver cells had disappeared.

The portal spaces throughout showed condensation of their reticulum and connective tissue stroma, but there was no evidence of fibroblastic proliferation.

An inflammatory cell infiltration of slight to fair intensity was seen in the portal areas. The infiltrating cells were chiefly lymphocytes and plasma cells with a moderate number of large mononuclear cells. Some of these contained small amounts of brown pigment. Polymorphonuclear leukocytes were lacking except where fairly extensive degeneration was taking place in the adjacent parenchyma.

The large bile ducts were not remarkable. The number of small perilobular bile ducts was increased, but these showed no active proliferation. Rarely these small ducts contained bile casts. Often a direct continuity could be seen between the perilobular bile ducts and groups or cords of liver cells.

The branches of the hepatic artery and the portal vein were not remarkable. The large efferent veins occasionally suggested slight fibrosis of their walls.

The spleen showed marked depletion of lymphoid tissue and diffuse fibrosis of the stroma.

In the esophagus the veins of the submucosa were widely dilated.

The duodenum displayed extensive old scarring involving all layers of the wall. A small active ulcer, extending into the submucosa, was present, but there was no evidence of hemorrhage.

In the lungs aspiration pneumonia and atelectasis were observed.

The kidneys showed some subacute and chronic pyelonephritis.

*Diagnosis.*—Cirrhosis of the liver, posthepatic; icterus; fibrosis of the spleen (280 Gm.); esophageal varices with erosion; hemorrhage, massive, into the gastrointestinal tract; duodenal ulcer, active, old; aspiration pneumonia; pulmonary atelectasis, and pyelonephritis, subacute and chronic were diagnosed.

CASE 2.—A 48 year old white carpenter was admitted to the hospital in October 1946. He complained of weakness of two to three years' duration and swelling

of the abdomen of three months, partly relieved by mercurial diuretics. He also had mild edema of the ankles, exertional dyspnea and moderate crampy pains in the upper abdominal region. For three years during the 1920's he had "drunk heavily"; he had stopped for a long time only to recommence five months before admission. His diet was always protein poor. The past history was unreliable; no account of previous jaundice or ascites was obtained.

He looked undernourished and slightly jaundiced. Three spider form telangiectases were seen on the anterior wall of his chest. There were basal rales in both lungs. The blood pressure was 150 systolic and 80 diastolic. The heart was normal. The abdomen was distended with fluid.

The urine had a specific gravity of 1.020 and contained bile, many erythrocytes, pus cells and a few granular casts. The patient was moderately anemic; his sedimentation rate (Westergren) was 110 mm. per hour. The white blood cells on admission numbered 4,350, with polymorphonuclears 67 per cent, "stab" forms 3 per cent, eosinophils 7 per cent, lymphocytes 22 per cent and monocytes 1 per cent. Serum proteins totaled 7 Gm. per hundred cubic centimeters of blood. The formaldehyde-gel test showed a positive reaction. The cephalin-cholesterol flocculation test was strongly positive on repeated occasions. The thymol turbidity test of the plasma was positive (33 units). The icterus index was 35. On admission there was no evidence of a tendency to bleed, but on the day of death (thirty-five days later) the clotting time (Duke method) was 12 minutes and the prothrombin time was 67 seconds—control, 32 seconds. The ascitic fluid was typical of a transudate. A roentgenogram of the upright abdomen was interpreted as showing nodularity of the liver.

The patient rapidly declined. His temperature, on admission 99.2 F., fluctuated daily between normal and 99.5 F. In his last week of life the jaundice intensified slightly and he became deeply comatose. His temperature dropped precipitously, and a day later he died.

*Autopsy.*—Gross Examination: The skin, the scleras and the conjunctivas were slightly icteric. The peritoneal cavity contained about 500 cc. of clear, yellowish green fluid. The liver weighed 1,350 Gm., and its surface was irregularly nodular. The nodules varied from 2 to 12 mm. in size and were generally yellowish tan and firm. Occasional nodules were either reddish brown or grayish yellow and soft. The tissue between the nodules was reddish and shrunken. The left lobe of the liver was atrophic and consisted merely of a thin lingula of reddish shrunken tissue with several nodules. The cut surfaces revealed similar nodules and complete loss of the lobular structure. The gallbladder was edematous but was otherwise not remarkable. The spleen weighed 560 Gm. and was firm. The malpighian corpuscles were indistinct, but the trabeculations were prominent. The esophagus showed dilation of the veins and several 1 to 2 mm. erosions, without evidence of hemorrhage. The duodenum and the proximal part of the ileum displayed edema. The mucosa of the distal part of the ileum was dark red and showed a few 1 to 2 mm. ulcerations. The mucosa of the colon was dark red in some areas. The small and large intestines contained large amounts of thick red fluid, which gave a positive reaction in the guaiac test. The combined weight of the kidneys was 435 Gm. The surfaces were finely and diffusely granular. The tips of the calices contained numerous tiny yellowish concretions. A small yellow granular stone was found in the left ureter where this passed through the wall of the bladder. The lungs showed atelectasis in both lower lobes. The bronchi contained much thick greenish mucus. Generalized arteriosclerosis was fairly marked.

**Microscopic Examination:** The liver showed complete loss of the lobular structure, with small nodules of parenchyma separated by varying-sized bands of stroma. Large areas were completely devoid of liver cells.

Peripherally in the nodules the liver cells tended to form wide, anastomosing cords, which on cross section were tubules with prominent central lumens. Toward the centers of the nodules the liver cells were haphazardly distributed.

The liver cells were larger than usual, and some contained two or three nuclei. The rather basophilic cytoplasm was finely granular. Rarely nuclei were vacuolated. In many nodules extensive degeneration of liver cells was seen, which involved chiefly the central and midzonal portions but often reached the periphery. Liver cells in varying stages of necrosis were seen. The contours of the necrotic cells could be discerned even in the most affected areas. There was little fatty metamorphosis and no hyaline degeneration. The uninvolved peripheral cells showed some regeneration.

The prominent bile canaliculi contained occasional bile casts.

The sinusoids in the necrotic areas were congested. Here hemorrhages and some infiltrations of polymorphonuclear leukocytes and rare large mononuclear cells were found. Elsewhere the sinusoids were not remarkable.

In the areas devoid of parenchyma the reticulum stroma was collapsed but showed the normal arrangement of parallel and cross fibers. The fibers appeared thickened, but there was no evidence of new formation of either reticulum or collagenous stroma. A similar condensation of the stroma without fibroblastic proliferation was seen in the portal spaces.

The portal spaces, as well as the areas depleted of parenchyma, showed some diffuse chronic lymphocytic and plasma cell infiltration. Polymorphonuclear leukocytes were present only in small numbers, except in areas adjacent to degenerating parenchymal nodules, where they were more numerous.

The small perilobular bile ducts were prominent, more numerous than usual and occasionally suggestive of proliferation. Some contained bile casts. These small bile ducts delineated the lobular contours in the areas from which the liver cells had disappeared. A direct continuity could be seen between these ducts and regenerated liver cells where these structures were found to abut. The larger bile ducts and the blood vessels were not remarkable.

The spleen displayed marked depletion of lymphoid tissue, congestion, and slight fibrosis of the stroma. The arteries and arterioles were sclerotic.

The esophageal and cardiac veins were dilated and congested.

The small intestine showed edema of the submucosa, with a moderate acute inflammatory cell infiltration. A small recent erosion was seen at the tip of a mucosal fold. The submucosal veins were dilated.

The large intestine also showed submucosal edema and congestion. Numerous small recent hemorrhages were present in the mucosa, which was ulcerated in these areas.

The kidneys displayed marked swelling of the tubular epithelium and some arteriosclerosis.

In the lungs marked atelectasis and congestion were found. The bronchi contained much mucus.

**Diagnosis.**—Cirrhosis of the liver, posthepatic; icterus; fibrosis of the spleen (560 Gm.); esophageal varices with erosions; phlegmonous enteritis, slight; edema and erosions of the colon; intestinal hemorrhage; ascites (500 cc.); tubular nephritis, mild; nephrolithiasis, bilateral; ureterolithiasis, left; pulmonary atelectasis and congestion, and generalized arteriosclerosis and arteriolosclerosis were diagnosed.

CASE 3.—A 53 year old white bricklayer was hospitalized in January 1947, complaining of abdominal swelling of two or three months' duration. In 1942 he was hospitalized because of an episode of jaundice and ascites. At that time his liver was enlarged, the icterus index was 17 and there was 1.8 mg. of bilirubin per hundred cubic centimeters of blood. A flat roentgenogram of the abdomen taken some three months after the onset of jaundice showed a nodular liver. The patient left against advice and was apparently well and on an adequate diet, but he continued to drink alcoholic beverages to excess, as he had done for many years. In November 1946, his abdomen again started to swell, his scleras became yellow, his urine dark and his stools light. Because of these signs, he was hospitalized.

He appeared chronically ill and was slightly jaundiced. The lungs were clear, and the heart was normal. The blood pressure was 120 systolic and 70 diastolic. The abdomen was markedly distended with fluid, and there was slight pitting pretibial edema.

The urine contained bile and urobilinogen in a dilution of 1:20 on admission, later in a dilution of 1:80. There was slight anemia (red cells hyperchromic). The sedimentation rate (Westergren) was 82 mm. in one hour. The white blood cells were normal. The serum proteins totaled 5.0 Gm. per hundred cubic centimeters, and the formaldehyde-gel test showed a positive reaction. The cephalin-cholesterol flocculation test showed a strongly positive result on repeated occasions, and the thymol turbidity test of the plasma was twice positive (32 and 38 units). The prothrombin time was normal on several occasions. The ascitic and pleural fluid (formed after admission) had the character of a transudate. Abdominal venography showed an unobstructed inferior vena cava.

The patient's course was steadily downhill. His only complaint was anorexia. His temperature, normal on admission, fluctuated from normal to 101 F. during the last week. Ascitic fluid formed as rapidly as it was removed. Vigorous attempts to supply his needs by oral and intravenous administration of protein failed. Evidence of phlebothrombosis appeared in the legs; ligation of both superficial femoral veins was done. The patient died in coma shortly thereafter, on the thirty-fourth day of hospitalization.

*Autopsy.*—Gross Examination: The scleras were slightly icteric. The peritoneal cavity contained about 3,000 cc. of dark amber fluid. The liver weighed 1,080 Gm. Its surface was studded with firm, yellowish tan nodules, varying from 1 to 15 mm. in size, between which small and larger areas of shrunken, reddish gray tissue were present. On the cut surface the centers of some nodules were gray or red. The intervening shrunken tissue showed complete loss of lobular structure. The gallbladder was edematous. The spleen weighed 570 Gm. and was firm. Its cut surface was dark red, with prominent trabeculae. The esophageal veins were dilated, and the cardiac mucosa showed two small areas of hemorrhage. Segments of the small and large intestines were edematous, but not otherwise remarkable. The combined weight of the kidneys was 455 Gm. On their cut surface the cortex was swollen, with some disappearance of landmarks. The left pleural space was largely obliterated by dense fibrous adhesions, but contained 1,100 cc. of amber fluid. About 500 cc. of similar fluid was found in the right pleural cavity. A recent infarct was present in the lower lobe of the left lung. The upper lobe of this lung and the lower lobe of the right lung showed atelectasis. Each groin showed the site of a recent ligation of the superficial femoral vein. A thrombus was found in the right femoral vein above the ligation. Dependent edema was present, more marked in the right leg and thigh. There was mild generalized arteriosclerosis.

**Microscopic Examination:** The liver had lost its lobular structure, and the liver cells formed small and large nodules separated by varying-sized bands or areas which were completely devoid of parenchyma.

In the nodules the liver cells showed generally a haphazard arrangement, with only slight tendency to align in cords at the periphery.

The liver cells were larger than usual and sometimes displayed two or three nuclei but did not form syncytia. The quite basophilic cytoplasm was finely granular.

Degenerative changes were prominent in many nodules, where they were seen chiefly in the central and midzonal areas. There was extensive fatty metamorphosis, which occasionally had progressed to complete necrosis. The necrotic cells, however, persisted in the involved areas, where their outlines could be discerned. The unaffected cells showed some regeneration.

Bile casts were encountered in occasional canaliculi, which were always prominent. These casts were best seen in the central clefts of liver cell cords in cross section.

The prominent congested sinusoids were generally not remarkable except in areas of necrosis, where they were disrupted. Recent hemorrhage with slight filtration of polymorphonuclear leukocytes and large mononuclear cells was seen in most areas of necrosis.

The reticulum stroma of the nodules was not remarkable. In the areas depleted of parenchyma the stroma preserved the lobular pattern without appreciable new formation of either reticulum or collagen. The stroma appeared condensed, with thickening of the individual fibers.

Similarly, the portal spaces failed to show any fibroblastic proliferation but displayed some chronic inflammatory cell infiltration (lymphocytes, plasma cells and rare large mononuclear cells).

The small perilobular bile ducts were numerous and often connected with regenerated liver cells. Rarely these ducts contained bile casts.

The larger bile ducts, as well as the blood vessels and lymphatic channels, were not remarkable.

The spleen showed marked depletion of lymphoid tissue and congestion, with fibrosis of the stroma.

The cardiac mucosa was ulcerated and showed an acute inflammatory cell infiltration. The submucosal veins were dilated.

Sections of small and large intestine revealed marked edema of the submucosa with diffuse acute inflammatory cell infiltration, which also involved the other layers.

The kidneys displayed swelling of the tubular epithelium.

In the lungs considerable chronic passive congestion and atelectasis were seen. One section showed part of a recent infarct.

*Diagnosis.*—Cirrhosis of the liver, posthepatic; icterus; fibrosis of the spleen (570 Gm.); esophageal varices with erosions; phlegmonous enterocolitis; ascites (3,000 cc.); edema, dependent; ligation of both superficial femoral veins post-operative, recent; thrombosis of the right femoral vein; pulmonary infarction; pulmonary congestion, marked; pulmonary atelectasis; hydrothorax (right, 500 cc.; left, 1,100 cc.); pleural adhesions, fibrous, of the left side; tubular nephritis, slight, and generalized arteriosclerosis, mild, were diagnosed.

**CASE 4.**—A 64 year old white carpenter was admitted April 16, 1947 and died forty hours later.

His last illness began about the first of January 1947, when he experienced a sudden onset of nausea and vomited large amounts of bloody material. He had

melenas for five to six days. A few days after the onset his abdomen began to swell for the first time, and his feet began to swell shortly thereafter.

The past history revealed that there had been moderate, but persistent, intake of alcoholic liquors ever since boyhood. He had always eaten well. Fifteen years previously he had jaundice and general malaise for about five weeks, after which he felt completely well until 1947.

With the aforementioned complaints he was hospitalized on Jan. 14, 1947, at which time physical examination revealed an afebrile, nonjaundiced man whose only abnormalities were ascites, enlargement of the spleen and moderate edema of the lower extremities.

The Kahn test of the blood was positive. The sedimentation rate (Westergren) was 109 mm. in one hour. He had a normocytic anemia, 1.2 per cent reticulocytes, 883,000 platelets and 3,100 white blood cells per cubic millimeter of blood on admission. The differential count was normal. The total white cell count varied from 2,100 to 3,100 during his hospital stay. The blood nonprotein nitrogen was normal. Serum proteins on admission totaled 6 Gm. per hundred cubic centimeters; this value rose to 7 Gm. The formaldehyde-gel test showed a positive reaction at all times (6 estimations). The cephalin-cholesterol flocculation test was persistently positive. The thymol turbidity test was twice positive (38 and 32 units). A test with sulfobromophthalein sodium (5 mg. per kilogram of body weight) showed 40 per cent retention after thirty minutes (the icterus index at this time was normal). The icterus index, which on admission was 15, had dropped to 5 at the time of discharge. The stool contained bile. The ascitic fluid had the character of a transudate. The bleeding, clotting and prothrombin times were normal. Swallowed barium sulfate revealed marked esophageal varicosities. A hippuric acid excretion test done five days before discharge produced 1.35 Gm. of hippuric acid (1.77 Gm. of sodium benzoate was given intravenously).

During a hospital stay of two months the patient improved markedly on a regimen which included a high protein diet with supplementary vitamins and choline, resting in bed, paracenteses, and the administration of mercurial diuretics. He was discharged on March 12, 1947, to regain strength. The plan was to readmit him to the surgical service for treatment of his esophageal varices.

During the interim the ascitic fluid collected fairly rapidly, but otherwise the patient felt well. On April 16, however, he vomited bright red blood, had a tarry bowel movement and became irrational. The next day he was readmitted to the hospital. At this time he was in shock. The temperature was normal, the pulse rate was 144 and the blood pressure was 80 systolic and 60 diastolic. There was no visible jaundice. The mucous membranes were pale. The lungs were clear and resonant. Marked ascites was present. The edge of the liver (felt after paracentesis) was hard and extended 3 cm. below the rib margin in the midline. Tarry feces were present in the rectum and gave a positive reaction in the guaiac test. There was no peripheral edema.

The urine was normal except for 2 to 5 hyaline casts per high power field. A Kahn test of the blood was negative. There were 2,560,000 red cells per cubic millimeter of blood and 6.8 Gm. of hemoglobin per hundred cubic centimeters of blood. The hematocrit reading was 22. The sedimentation rate was 17 mm. in one hour. There were 8,150 white cells per cubic millimeter, with a normal differential count.

The patient was given sedative treatment and two transfusions of 500 cc. of whole blood, but the shock persisted. About twenty-four hours after admission he vomited 150 cc. of dark red blood. He died in coma forty hours after admission.

*Autopsy.*—Gross Examination: The peritoneal cavity contained 1,800 cc. of cloudy amber fluid. The liver weighed 1,520 Gm., and its surface was irregularly



nodular. The nodules were yellowish tan or reddish brown and firm and varied from 1 to 20 mm. in size. Between the nodules were varying-sized areas of shrunken, reddish gray tissue which lacked any trace of lobular pattern. The right lobe of the liver contained near its diaphragmatic surface a 3 cm. cyst filled with dark brown granular material. The cut surfaces revealed complete loss of lobular structure and presence of nodules of the already described appearance set against a background of shrunken parenchyma. The portal and hepatic veins were not remarkable. The gallbladder and the bile ducts were normal. The spleen weighed 650 Gm., was firm and displayed a uniformly dark red cut surface. The esophageal veins were distended. The stomach and the intestines contained large amounts of thick reddish material, which gave a positive reaction in the guaiac test. Segments of the small and large intestines were edematous. The combined weight of the kidneys was 330 Gm. Each pleural cavity contained about 200 cc. of fluid. Areas of bronchopneumonia were noted in both lungs. The aorta, as well as the larger arteries, showed marked arteriosclerosis. Permission to examine the central nervous system was not granted.

**Microscopic Examination:** The liver showed complete loss of lobular structure. Small and large nodules of haphazardly arranged liver cells were separated by bands or wide areas which were devoid of parenchyma. The liver cells were larger than normal; sometimes they were multinucleated and occasionally they formed syncytia. The intercellular bile canaliculi were prominent but did not contain bile casts.

Except for patchy areas of fatty metamorphosis occurring chiefly in the central and midzonal portions of the nodules, no degenerative changes were noted.

A number of nodules in sections taken from widely separated portions of the liver were composed of neoplastic cells, which, however, closely reproduced the structure and the cytologic characteristics of liver cells. The tumor cells were arranged in abortive columns and cords, which commonly displayed a central cleft or channel. Between the cells intercellular bile canaliculi might be seen, which sometimes contained definite bile casts. The cells and their nuclei displayed definite pleomorphism and frequently formed syncytial masses. The round or oval nuclei were large and vesicular, with generally one prominent nucleolus, which was eccentrically placed near the nuclear membrane. Rare mitoses were present. The cytoplasm was ample, granular and markedly basophilic. Many cells displayed multiple fat droplets, which did not displace the nuclei. In addition, many tumor cells exhibited in their cytoplasm prominent dense acidophilic masses of round or oval shape. Hemorrhage and necrosis of the neoplastic tissue were observed only in the sections of the cystic area described. Invasion of larger blood vessels by tumor was not observed, but small groups of neoplastic cells were commonly present around the larger tumor nodules.

The tumor masses possessed a well formed reticulum framework and a rich sinusoidal blood supply, both of which were quite similar to those of the non-neoplastic nodules of the liver.

The large tumor nodules were surrounded in a capsule-like fashion by condensed hepatic stroma, which displayed some proliferation of connective tissue. Many of the smaller neoplastic masses lacked capsules but compressed the surrounding liver cells.

Away from the neoplastic masses the stroma in the often quite extensive areas devoid of parenchyma was condensed, with thickening of the fibers, but the stromal structure of the original collapsed hepatic lobules persisted without new formation of either reticulum or collagen. The portal spaces showed no scarring and were infiltrated by small numbers of lymphocytes and plasma cells.

The small perilobular bile ducts were increased in number and were often seen to connect with the liver cells. The larger bile ducts were not abnormal.

The sinusoids of the hepatic nodules, as well as the larger blood vessels and the lymphatic channels, were not remarkable.

The spleen showed fibrosis of the stroma, congestion, and depletion of lymphoid tissue.

The cardiac veins were widely dilated. Sections of the small and the large intestine showed edema of the submucosa with diffuse acute inflammatory cell infiltration, which also involved other layers.

The kidneys revealed some arteriosclerosis.

The lungs showed bronchopneumonia, edema and congestion. No tumor metastases were found.

*Diagnosis.*—Cirrhosis of the liver, posthepatic; hepatocellular carcinoma of the liver; fibrosis of the spleen (650 Gm.); esophageal varices; hemorrhage in the gastrointestinal tract; phlegmonous enterocolitis; ascites (1,800 cc.); bilateral hydrothorax (200 cc.); bronchopneumonia; pulmonary edema, and generalized arteriosclerosis were diagnosed.

CASE 5.—A 53 year old Negro laborer who suffered from chronic alcoholism and gave a poor dietary history was admitted on June 6 and died on June 19, 1947.

In 1937 he was hospitalized for a month because of intermittent epigastric pain, sense of fulness and nausea of one year's duration. He was jaundiced and had ascites, and the liver was enlarged and tender. The icterus index was 80. The urine contained bile and urobilinogen. A Wassermann test of the blood was negative. The sedimentation rate was 19 mm. in one hour. He improved gradually and went back to work, although he never felt completely well again.

In 1944, when he was admitted because of myocardial infarction, the liver was felt 2 to 3 fingerbreadths below the costal margin. He was not anemic. No studies of liver function were made.

In 1945 he again began to have nausea following ingestion of fatty foods. This persisted and in 1946 was accompanied by epigastric pain. In February 1947 he was rehospitalized. For two months preceding his admission he had aching in the right upper abdominal quadrant and abdominal swelling. At this time examination disclosed enlargement and tenderness of the liver, which was smooth and firm, moderate splenomegaly, mild edema of the ankles and evidence of hypertensive, arteriosclerotic cardiovascular disease. The red and white blood cell counts were normal. The sedimentation rate was 107 mm. in one hour. The urine contained urobilinogen (1:50). There was 40 per cent retention of sulfobromophthalein (test dose, 5 mg. per kilogram) at thirty minutes on two occasions. Serum proteins totaled 6 Gm. per hundred cubic centimeters on admission and 7.4 Gm. a month later; the formaldehyde-gel test showed a positive reaction both times. His icterus index was 13. The cephalin-cholesterol flocculation test was constantly positive, and the thymol turbidity test of the plasma was positive (23 units). The bleeding, clotting and prothrombin times were normal. Needle biopsy of the liver resulted in a diagnosis of posthepatic cirrhosis. He had several bouts of unexplained fever lasting three and four days. Despite his resting in bed and adhering to a high protein diet with vitamin supplements and choline, he did not improve and was discharged after a two months' stay.

He existed at this level for about a month. Then his abdomen began to swell, and his weakness increased. This led to his final admission. At this time he was moderately jaundiced. A spider form angioma was noted on his left shoulder. There was right hydrothorax. The liver, which was palpable 3 fingerbreadths

below the costal margin, was hard and tender. There was moderate ascites, also edema of the ankles. During the previous four months he had become remarkably emaciated. The urine contained bile and urobilinogen. He had 13.5 Gm. of hemoglobin per hundred cubic centimeters and 7,000 white blood cells per cubic millimeter of blood, with a normal differential count. The sedimentation rate was 64 mm. in one hour. The icterus index was 22 on this admission; the cephalin-cholesterol flocculation test was positive. The thymol turbidity test of the plasma was positive (37 units). The serum proteins totaled 7 Gm. per hundred cubic centimeters. The formaldehyde-gel test was positive. The icterus index rose to 46 and then to 60 two days before death. On the day before death his prothrombin time was equal to that of a 20 per cent normal control. His course proceeded downhill. He had severe abdominal pain and bloody diarrhea lasting five days, became comatose, and died on the twelfth hospital day.

*Autopsy.*—Gross Examination: The scleras were icteric. The peritoneal cavity contained 300 cc. of clear amber fluid. The liver weighed 3,260 Gm. and was irregularly nodular. The hepatic nodules ranged from 3 to 15 mm. in size and were soft and yellowish brown. Between the nodules narrow or wide bands of shrunken, reddish gray tissue were present. The lateral and diaphragmatic aspect of the right lobe contained a large, soft mass. In this area the surface of the organ showed yellowish red nodules ranging from 20 to 50 mm. in size. The cut surfaces of this portion of the liver revealed a soft, greenish yellow, multinodular tumor mass, about 12 cm. across, which displayed several dark red areas of necrosis. The cut surfaces of the rest of the organ showed complete loss of normal structure with nodules of yellowish brown parenchyma against a background of varying-sized, often extensive areas of shrunken tissue. The hepatic veins, as well as a major branch of the portal vein, were invaded by tumor. The gallbladder and the bile ducts were not remarkable. The spleen weighed 470 Gm. and was firm. Its cut surfaces were deep reddish brown, with indistinct malpighian corpuscles and prominent trabeculae. No esophageal varices were found. The small and large intestines were edematous in areas, but there was no hemorrhage. Each pleural cavity contained about 100 cc. of clear fluid. The lungs were studded with many yellow, soft nodules ranging from 1 to 20 mm. in size. The combined weight of the kidneys was 235 Gm. On their cut surface the usual landmarks were indistinct. The heart weighed 330 Gm. and showed an area of old fibrosis, 10 by 20 mm. in diameter, in the interventricular septum just beneath the aortic ring. The coronary arteries were somewhat sclerosed. There was some generalized arteriosclerosis. The brain showed no metastases.

Microscopic Examination: The liver consisted of small and large nodules of parenchymal cells scattered in a background of stroma which in many areas was completely devoid of liver cells.

The liver cells were large, often multinucleated, and frequently formed syncytial masses. The intercellular bile canaliculi were prominent and often contained bile casts.

Many hepatic nodules displayed degenerative changes, which occurred mostly in the central and midzonal areas but sometimes involved the peripheral zones. The changes consisted chiefly of fatty metamorphosis, but areas of necrosis of liver cells were also present. The remnants of the necrotic cells persisted in the involved areas, where a slight to moderate concentration of neutrophilic polymorphonuclear leukocytes and some extravasation of red blood cells were seen. In these areas the Kupffer cells were prominent and displayed phagocytosis. The liver cells peripheral to the necrotic areas showed some regeneration.

Sections taken from the mass in the right lobe of the liver displayed nodules of neoplastic cells which, despite considerable anaplasia, closely resembled liver cells. The tumor cells tended to arrange themselves in bizarre columns, in which there were central clefts. Between the cells distinct intercellular bile canaliculi were often seen, and these frequently contained bile casts. The neoplastic cells were large, with ample cytoplasm which was granular and quite basophilic. The vesicular nuclei tended to be round or oval and frequently had multiple prominent nucleoli, which were placed eccentrically, near the nuclear membrane. Mitoses were frequent and sometimes atypical. Fat vacuoles were present in some tumor cells, and there were many areas of necrosis, accompanied by some hemorrhage and slightly infiltrated by neutrophilic polymorphonuclear leukocytes. Tumor invasion of blood vessels was noted in many instances. A well formed but delicate reticulum framework and an ample sinusoidal blood supply were observed in the tumor masses. The neoplastic cells freely invaded the surrounding tissue.

The tumor nodules, as well as the nodules of non-neoplastic liver cells, were set in a background of condensed hepatic stroma, which in many and often rather extensive areas was devoid of liver cells. The original lobular pattern of the stroma remained unaltered. The individual fibers appeared thickened, but there was no new formation of either reticulum or collagen in these areas. The portal spaces were approximated in consequence of the collapse of the liver lobules. They were infiltrated by small numbers of chronic inflammatory cells. Only near areas of necrosis might a slight concentration of neutrophilic polymorphonuclear leukocytes be found.

The small perilobular bile ducts were numerous and were often continuous with the liver cells at the peripheries of the non-neoplastic nodules. The large bile ducts were not remarkable.

The sinusoids were markedly congested. The large blood vessels and lymphatic channels were not remarkable except for occasional tumor invasion of the former.

The spleen showed fibrosis, congestion and depletion of lymphoid tissue.

The lungs displayed numerous metastatic tumor nodules identical with those found in the liver. The tumor cells were seen to produce bile in some instances. Small groups and large masses of neoplastic tissue were seen in many blood vessels. Some early bronchopneumonia was also present.

The cardiac veins were somewhat dilated. The small and large intestines showed some edema of the submucosa.

The kidneys revealed swelling of the tubular epithelium as well as some arterial and arteriolosclerosis.

The heart showed small patchy areas of old fibrosis. Sections from the area in the interventricular septum described in the gross specimen showed complete replacement of the myocardium by dense connective tissue. The branches of the coronary artery were sclerotic.

Diagnosis: Cirrhosis of the liver, posthepatic; hepatocellular carcinoma of the liver with pulmonary metastases; icterus; fibrosis of the spleen (470 Gm.); ascites (300 cc.); hydrothorax (100 cc. bilaterally); segmental edema of the intestines; myocardial infarction, healed; myocardial fibrosis; generalized sclerosis of arteries and arterioles; bronchopneumonia, and tubular nephritis, mild, were diagnosed.

#### COMMENT

The clinical picture in these cases was that of hepatic failure with portal hypertension. Icterus and ascites were present in all, ascites in 4, and severe gastrointestinal bleeding in 3. Laboratory findings indicative of hepatic failure were present in all. Although there was no doubt as to

the presence of hepatic failure, the pathologic basis of the process could not be determined by physical or laboratory findings.

The histories of 4 patients, however, suggested previous episodes of hepatitis. Hepatitis was observed to develop in the first patient eight months after a transfusion and five years before her final admission. The first episode of hepatitis was prolonged, and even after subsidence of jaundice, studies of liver function showed appreciable impairment. Another bout occurred a year later, at which time hepatic function was again shown to be poor. This history is consistent with post-transfusion hepatitis.<sup>11</sup> The third patient was seen in 1942 because of jaundice, ascites and evidence of severely impaired hepatic function. His clinical picture was compatible with severe hepatitis.<sup>21</sup> The long symptom-free interval makes it more likely that the preceding episode represented hepatitis rather than decompensated Laennec's cirrhosis. The past histories of the fourth and fifth patients are essentially similar, episodes consistent with hepatitis having occurred fifteen and ten years, respectively, before the condition progressed to fatal liver failure.

The second patient's history, on the other hand, reveals no evidence of previous hepatitis. His case is included because the autopsy revealed changes strikingly similar to those noted in the other 4 patients. The other patients were observed in the Grady Memorial Hospital and its clinics for many years and gave no history of having been exposed to drugs or poisons. The second, third, fourth and fifth patients suffered from chronic alcoholism.

The livers of all the patients were strikingly similar in their morphologic aspects and differed even on gross examination from the liver characteristic of Laennec's cirrhosis.

The weights of the livers of the first 3 patients ranged from 900 to 1,350 Gm. The surfaces were studded with firm yellow-tan nodules varying in diameter from 1 to 20 mm. Some nodules were soft and gray or red. Between the nodules in areas often several centimeters in diameter the tissue was shrunken and reddish gray. In the second patient the left lobe of the liver was atrophic and consisted of shrunken, reddish tissues with a few nodules. The cut surfaces showed the nodules against a background of atrophic tissue. The lobular structure was completely lost.

The gross appearance of the liver of the fifth patient, which weighed 3,260 Gm., was complicated by a superimposed primary liver cell carcinoma, which invaded the hepatic veins as well as a main branch of the portal vein. In this case the neoplasm was readily recognized, but in the gross examination of the liver of the fourth patient, which weighed 1,520 Gm., the presence of a tumor was not suspected. Otherwise these 2 livers were identical in gross appearance with the others.

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21. Soffer and Paulson.<sup>3</sup> Kelsall and others.<sup>21</sup> Fearnley.<sup>10</sup>



Fig. 1.—*A*, nodule of liver against a background of stroma devoid of liver cells; phloxine-methylene blue;  $\times 105$ . The parenchymal cells form irregular, anastomosing cords. The intercellular bile canaliculi are prominent.

*B*, small nodule of regenerated liver cells surrounded by newly formed small bile ducts; phloxine-methylene blue;  $\times 330$ .



Fig. 2.—*A*, regenerated liver cells; phloxine-methylene blue;  $\times 330$ . The intercellular bile canaliculi contain bile casts. The cross section of a liver cell multinucleated liver cell is shown left of center.

*B*, degenerative changes in a liver nodule; phloxine-methylene blue;  $\times 85$ . These changes occurred chiefly in the central and midzonal areas.



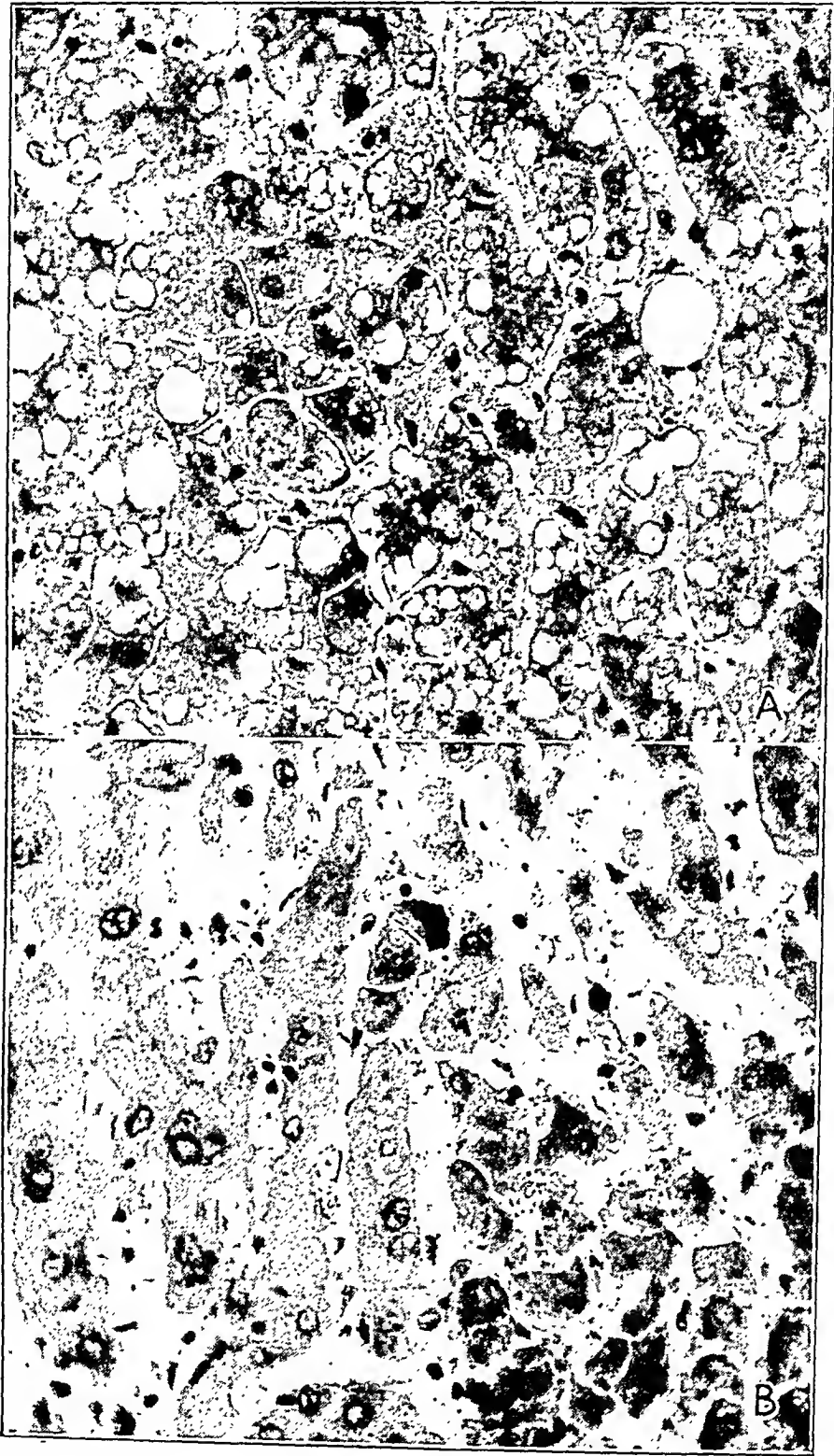


Fig. 3.—*A*, fatty metamorphosis of regenerated liver cells; phloxine-methylene blue;  $\times 330$ .

*B*, varying stages of necrosis of regenerated liver cells; phloxine-methylene blue;  $\times 330$ . The cells on the right side of the field are completely necrotic, but note that they persist.



Histologic examination showed small and large nodules of liver cells separated by bands and wide areas of stroma devoid of liver cells (fig. 1*A*). The nodules lacked a lobular pattern and were surrounded by many prominent small bile ducts (fig. 1*B*). The liver cells had obviously formed by regeneration. The cells varied in size, and multinucleated cells, as well as syncytial masses, were common. The intercellular bile canaliculi were prominent and often contained bile casts (fig. 2*A*). Degenerative changes of varying, often considerable, extent involved the liver cells (fig. 2*B*). They occurred chiefly in the centers and midzones of the nodules but sometimes extended to the peripheries. The changes ranged from fatty metamorphosis (fig. 3*A*) to necrosis, leaving behind the ghostlike outlines of the necrotic cells (fig. 3*B*). A mild infiltration of inflammatory cells (large mononuclear cells and polymorphonuclear leukocytes) accompanied these changes.

In the areas devoid of liver cells the stroma showed preservation of the lobular pattern (fig. 4*A*). The fibers were condensed and thickened, but the normal pattern of the stroma was unaltered (fig. 4*B*). No new formation of either reticulum or stroma could be observed. The contours of the collapsed liver lobules were delineated by the small perilobular bile ducts, which were increased in number and prominent (fig. 5*A*). The portal spaces showed no scarring, and there was only a mild degree of chronic inflammatory cell infiltration. The primary liver cell carcinoma observed in 2 cases presented a typical picture (fig. 5*B*). The tumor cells closely reproduced liver cells with intercellular bile canaliculi and actual formation of bile. The stroma of these tumors was a delicate reticulum framework with a rich sinusoidal blood supply. Pulmonary metastases were present in the fifth patient.

The findings in the other organs were those of portal hypertension and obstruction. Congestion and fibrosis of the spleen were noted in all patients, and esophageal varices were present in all but the fifth patient. Phlegmonous enterocolitis was observed in the second, third and fourth patients and segmental edema of the intestines in the first and fifth. Gastrointestinal hemorrhage had occurred in the first, second and fourth patients. In the first patient an old duodenal ulcer was present but was not the source of the hemorrhage.

Ascites was found in all but the first patient. Icterus was present in all but the fourth and appeared to result from obstruction of the small bile canaliculi within the parenchymatous nodules.

Our findings were quite similar to those described by Lucké in sub-acute infectious hepatitis. They differed from those of acute infectious hepatitis only in these points: The rapid death of liver cells and the

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22. Mallory, T. B.: The Pathology of Epidemic Hepatitis, *J. A. M. A.* **134**: 655-661 (June 21) 1947.

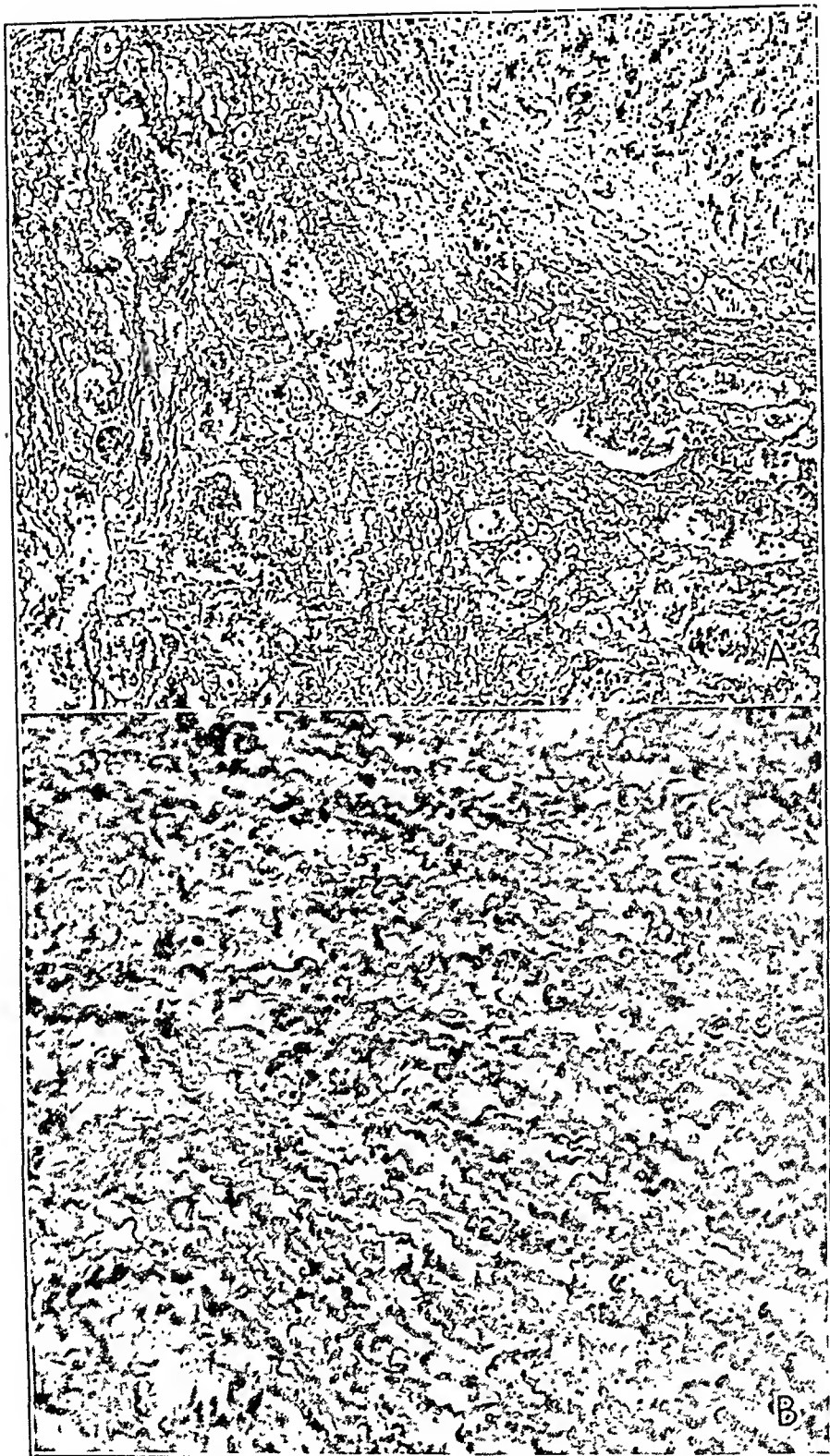


Fig. 4.—*A*, collapsed reticulum framework of an area devoid of parenchyma; Wilder's reticulum stain;  $\times 80$ . A nodule of regenerated liver cells is shown in the right upper corner.

*B*, high power view of the reticulum stroma in an area devoid of parenchyma; Wilder's reticulum stain;  $\times 365$ . The individual fibers are thickened, but the normal arrangement of parallel and oblique fibers is preserved.

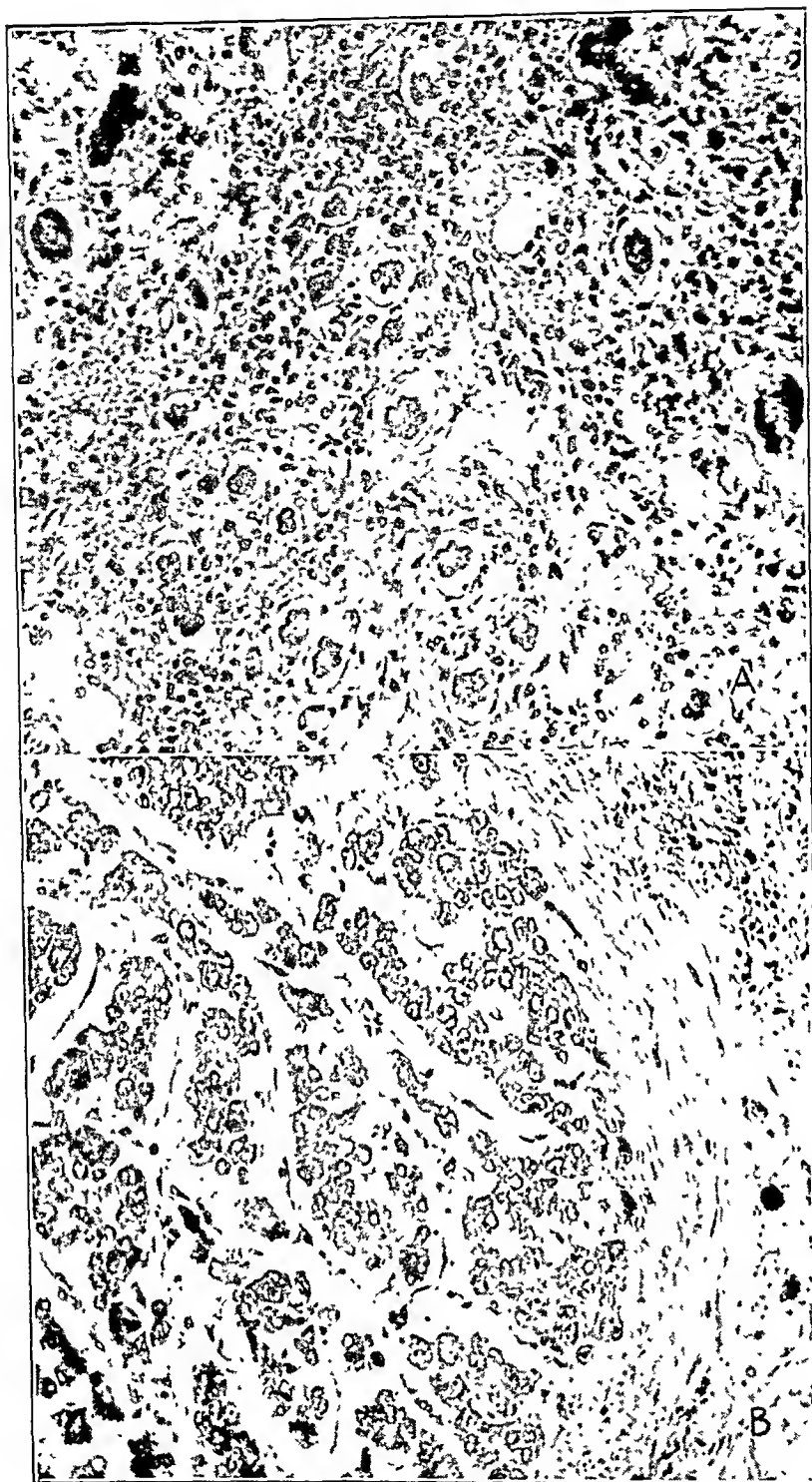


Fig. 5.—*A*, contours of the vanished hepatic lobules outlined by the numerous newly formed small perlobular bile ducts; phloxine-methylene blue;  $\times 160$ . There is no significant inflammatory cell infiltration.

*B*, primary liver cell carcinoma; phloxine-methylene blue;  $\times 160$ . The neoplastic cells form cords and display a sinusoidal blood supply.

speedy removal of cellular debris which are characteristic of the acute stages of hepatitis seen at autopsy<sup>22</sup> were no longer present in our cases. By the same token, the inflammatory cell infiltration was chronic and not particularly active. On the other hand, degenerative changes were present in the regenerated liver cells in a varying but always appreciable degree. They could be traced through all phases from fatty metamorphosis to necrosis, and thereby the progressive character of the lesion was indicated. In Lucké's cases of subacute infectious hepatitis the liver displayed only a few areas of degeneration of this type and was said to show no evidence of progressive destruction of tissue.

Because of the active degenerative changes observed in our cases, we consider the lesion to have been progressive. The clinical course in our cases certainly agrees with this conclusion.

The mechanism of these degenerative changes is not understood. Lucké considered them probably secondary to ischemia and accumulation of metabolic products. One could also speculate that in liver cells which have regenerated in an infected organism a degree of adaptation has occurred between virus and host cells in some cases. Instead of rapidly dying, as in the fulminant form of the disease, or being completely restored on recovery as in most cases, the parenchymal cells may gradually degenerate in a few instances. The disease may then have a chronic progressive course. The resemblance observed between our findings and those of prolonged infectious hepatitis was striking. In fact, a chronic form of infectious hepatitis may account for this picture without the addition of secondary changes.

Our findings are not only similar to those described as occurring in infectious hepatitis, a disease termed in the past idiopathic acute yellow atrophy,<sup>23</sup> but they seem to us identical with those described by F. B. Mallory as seen in "toxic cirrhosis" in 1911<sup>24a</sup> and as "healed acute yellow atrophy" in 1932.<sup>24b</sup>

Karsner<sup>25</sup> preferred to call this lesion "post-necrotic cirrhosis" and stated that it follows various infectious diseases and injuries caused by certain poisons and drugs, as well as acute yellow atrophy. The latter is now known to be merely a designation of acute hepatic failure, whatever the cause.<sup>26</sup> Acute diffuse necrosis of liver cells, i.e., hepatitis, is

23. Case Records of the Massachusetts General Hospital, Case 28391, *New England J. Med.* **227**:485-487 (Sept. 24) 1942.

24. Mallory, F. B.: (a) Cirrhosis of the Liver: Five Different Types of Lesions from Which It May Arise, *Bull. Johns Hopkins Hosp.* **22**:69-75 (March) 1911; (b) Cirrhosis of the Liver, *New England J. Med.* **206**:1231-1239 (June 16) 1932.

25. Karsner, H. T.: Morphology and Pathogenesis of Hepatic Cirrhosis, *Am. J. Clin. Path.* **13**:569-606 (Nov.) 1943.

26. Acute Yellow Atrophy of the Liver, editorial, *J. A. M. A.* **133**:1156-1157 (April 12) 1947.

acknowledged to precede postnecrotic cirrhosis. The belief that bacterial toxins are involved in the production of this necrosis has been superseded by the recognition of a viral factor. Certain chemicals are known to produce this type of necrosis. We believe that in order to assign a chemical cause a definite history of exposure must be obtained. This is lacking in our cases.

Popper and Franklin<sup>27</sup> have recently stated that the morphologic picture of acute viral hepatitis differs from that of "toxic hepatitis." This interesting observation deserves further investigation, particularly with regard to possible differences in the progress and the end results of the tissue changes.

The lesion in our patients differed from other types of cirrhosis. The principal distinction was that the lobular pattern of the stroma had been preserved in the areas devoid of parenchyma without new formation of either reticulum or collagen. The varying-sized, often extensive areas of collapsed stroma separated islands of regenerated liver cells, which were irregularly distributed. The singular lack of stromal involvement has never been explained.

These features had been clearly defined by F. B. Mallory,<sup>24</sup> who stressed that the increase of the connective tissue in "toxic cirrhosis" was apparent rather than real. This he contrasted with other types of cirrhosis, particularly Laennec's, in which he emphasized the proliferation of fibroblasts resulting in actual increase of connective tissue.

F. B. Mallory<sup>24</sup> and Connor,<sup>28</sup> as well as Wilson and Goodpasture,<sup>29</sup> stated that the morphologic picture of "toxic cirrhosis" was sufficiently distinct to permit its identification. Karsner concluded that in typical cases "postnecrotic cirrhosis" may be easily recognized but doubted that this would be possible in borderline cases.

Cirrhosis of the liver has been recently defined<sup>25</sup> as a diffuse progressive chronic inflammation accompanied by fibrosis (i.e., new formation of connective tissue), retrogressive changes in the parenchyma and proliferation of remaining cells in the direction of regeneration. How, then, can we apply the term of cirrhosis to a hepatic lesion the diagnosis of which requires the absence of new formation of reticulum and collagen? In fact, we have speculated that this lesion may be nothing but an extremely protracted form of infectious hepatitis. The existing information about the natural history of infectious hepatitis invites such speculation, but present knowledge cannot confirm it.

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27. Popper, H., and Franklin, M.: Infectious Hepatitis Contrasted with Toxic Hepatitis, *Proc. Inst. Med. Chicago* **16**:353-354 (March 15) 1947.

28. Connor, C. L.: Toxic Cirrhosis of the Liver, *Canad. M. A. J.* **17**:546-551 (May) 1927.

29. Wilson, J. D., and Goodpasture, E. W.: Yellow Atrophy of the Liver, Acute, Subacute and Healed, *Arch. Int. Med.* **40**:377-385 (Sept.) 1927.

The term "cirrhosis" could be retained for the lesion we describe in conformity with the definition of F. B. Mallory, who applied the term to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue. This definition does not require actual formation of connective tissue as an essential part of cirrhosis and is completely satisfied by the lesion we report. In fact, this lesion is identical with the "toxic cirrhosis" described by him.

In all our cases the clinical picture was consistent with that of Laennec's cirrhosis terminating either in hepatic failure or conditions associated with portal hypertension. However, we believe that all clinical data except those of biopsy of liver (which was diagnostic in the fifth case) are of uncertain value in differentiating long-standing infectious hepatitis from decompensated Laennec's cirrhosis. Therefore, we base our conclusions on morphologic findings. We think it probable that the hepatic lesion observed in our patients was the end result of infectious hepatitis. The problem of the end result of infectious hepatitis is now of special importance because of the size of the recent epidemics.

#### SUMMARY

Five patients were studied whose terminal illness was either hepatic insufficiency or a complication caused by portal obstruction. Three of these patients were studied repeatedly in the course of several years. In 4 patients the terminal clinical picture was identical with that of Laennec's cirrhosis, and in the other, with that of rapid hepatic failure.

Morphologic studies revealed a chronic progressive injury of the liver, complicated in 2 cases by superimposed primary liver cell carcinoma. The changes observed in our cases not only were identical with the lesion described in the past as toxic or postnecrotic cirrhosis or as healed acute yellow atrophy but bore a close resemblance to the changes in the subacute infectious hepatitis studied intensively in recent years. We suggest that the lesion which we encountered may be a chronic form of infectious hepatitis.

## MASSIVE PICROTOXIN THERAPY IN TREATMENT OF ACUTE BARBITURATE POISONING

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AND  
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THE PURPOSE of this presentation is to describe our experience in the treatment of acute barbiturate intoxication with massive doses of picrotoxin in 30 cases. These cases were seen since Jan 1, 1946.

The treatment of barbiturate poisoning has been extensively discussed in the literature with various therapeutic procedures recommended, depending on the drug of choice. We have selected 11 severe cases from our series to demonstrate the massive therapy employed. In 2 of the selected cases doses of picrotoxin greater than any previously recorded in the literature were given.<sup>1</sup>

It is usually difficult to determine the amount of barbiturate consumed and the time elapsed before hospitalization, so that the severity of the poisoning must be judged from the initial observations and the subsequent course. We considered intoxication to be severe: (1) when more than 1 to 2 Gm. of a barbiturate was ingested; (2) when unconsciousness prior to hospitalization was prolonged; (3) when coma was associated with absence of reflexes, and (4) when respiratory depression was present.

On the patient's admission to the hospital a rapid appraisal was made of his condition and depth of unconsciousness. This appraisal included principally a neurologic examination, determination of blood pressure and examination for signs of inadequate respiratory exchange, such as

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From Michael Reese Hospital.

1. Richards, R. K., and Menaker, J. G.: The Role of Picrotoxin in the Treatment of Acute Barbiturate Poisoning, *Anesthesiology* **3**:37-47 (Jan.) 1942. Boyd, E. M.: Picrotoxin for Barbiturate Poisoning, *Canad. M. A. J.* **54**:442-443 (May) 1946. Anderson, J. P.: Treatment of Barbiturate Intoxication, with Specific Reference to Picrotoxin: Report of Twenty Cases, *Ann. Int. Med.* **14**:2037-2046 (May) 1941. Billow, B. W.: Barbiturate Intoxication and Picrotoxin Treatment, *J. Lab. & Clin. Med.* **29**:263-269 (March) 1944. Dorsey, J. F.: The Picrotoxin Treatment of Barbiturate Poisoning, *J. Nerv. & Ment. Dis.* **99**:367-375 (April) 1944. Russo, J., and Nicholson, M.: The Treatment of Barbiturate Overdosage, *Lahey Clin. Bull.* **4**:246-251 (April) 1946. Burdick, D. L., and Rovenstine, E. A.: Picrotoxin in Barbiturate Poisoning, *Ann. Int. Med.* **22**:819-826 (June) 1945. Treatment of Barbiturate Poisoning, *Conferences on Therapy, Am. J. Med.* **1**:93-103 (July) 1946.

pharyngeal and tracheal obstruction or cyanosis. The immediate therapy was based on findings from these examinations. General supportive measures were instituted at once. Respiratory embarrassment and peripheral circulatory collapse were treated in the orthodox manner, i.e., with provision of an adequate airway (nasal or endotracheal), oxygen inhalations and intravenous administration of fluids. For several patients with respiratory depression the use of artificial respiration was necessary in conjunction with the administration of respiratory stimulants and analeptic drugs.

Gastric lavage was performed for most of these patients, in spite of the fact that they were unconscious many hours prior to admission. While the gastric tube was in place a saline cathartic was frequently administered. Samples of the gastric juice and urine were tested for barbiturates. If there was any doubt of the diagnosis, a spinal puncture was performed in an attempt to rule out any other intracranial pathologic condition, e.g., hemorrhage.

Frequent aspiration of mucus from the throat was continued as long as the patient was unconscious. The Trendelenburg position was often useful in preventing aspiration of secretions. Because of the high incidence of pulmonary complications, penicillin therapy was instituted for these patients from the time of their admission, even though they were afebrile and presented no signs of such a complication. Frequent turning of the patient in bed was also helpful in this regard.

Analeptic drugs are the vital part of therapy in severe barbiturate intoxications. Picrotoxin was used almost exclusively for our patients, although at times it was supplemented with "metrazol" desoxyephedrine hydrochloride and amphetamine. Goodman and Gilman<sup>2</sup> discussed the pharmacologic properties and modes of action of these drugs. In our series the method of administration was not unique, but much larger doses of analeptic substances were used than are ordinarily recommended in the literature. The individual dose of picrotoxin for these patients varied. Amounts ranging from 9 to 45 mg. per dose given intravenously at fifteen-minute intervals were necessary to obtain the desired degree of stimulation. Once intravenous administration of fluids was started, all medicaments were injected into the rubber tubing to save veins for future use and to avoid excessive trauma. As the patients improved, the amount of drug was progressively decreased, according to the irritable response obtained from the picrotoxin. After muscular twitching was once obtained, the therapy revolved about maintenance of constant irritability and twitching just below the convulsive threshold. In spite of

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2. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students*, New York, The Macmillan Company, 1941.



all precautionary measures, however, many of the patients had short convulsions; there were apparently no untoward effects from these episodes.

Recent literature advocated the use of amphetamine as an antidote for barbiturate overdosage. Freireich and Landsberg,<sup>3</sup> reporting on this subject, stated they used the drug in a series of cases, their largest total dose being 400 mg. In several of the cases reported in the present paper, amphetamine was used with the picrotoxin. The chief rationale for the use of amphetamine was that it stimulated the depressed cerebral cortex, thereby supplementing picrotoxin, which acts mainly on the lower brain centers.

A third analeptic agent, "metrazol," has also been employed as a stimulant of the central nervous system.<sup>4</sup> The rapid response to this drug may be utilized as an aid in the determination of the depth of coma. At periodic intervals while patients were receiving active picrotoxin therapy, we gave 1 cc. (100 mg.) of "metrazol" intravenously and observed the response. If no reaction was elicited, the dose was progressively increased to 3 cc. and the response was graded accordingly; thus, a crude estimate of the degree of depression of the central nervous system could be made. This method was reported by Alexander,<sup>5</sup> who used 4 cc. of "metrazol" and classified the patients into four grades according to their response.

The presence of peripheral vascular collapse was a common complication in the severer intoxications. It may be seen from the table that 5 patients showed a dramatic fall in blood pressure. The therapeutic agents employed, besides analeptic stimulants, included plasma, isotonic solution of sodium chloride and whole blood, the amount depending on the patient's condition. A recent addition to these chemotherapeutic agents was desoxyephedrine hydrochloride, which was used both for its stimulating action on the central nervous system and for its effect of raising blood pressure.

#### REPORT OF CASES

CASE 5.—A 24 year old white woman ingested 100 grains (6.48 Gm.) of phenobarbital and was not hospitalized until after eighteen hours of unconsciousness. On her admission, physical examination showed her blood pressure to be

3. Freireich, A. W., and Landsberg, J. W.: Amphetamine (Benzedrine) Sulfate for Acute Barbiturate Poisoning, *J. A. M. A.* **131**:661-663 (June 22) 1946.

4. Androp, S.: The Use of Metrazol in Barbiturate Poisoning, *Psychiatric Quart.* **18**:13-22 (Jan.) 1944.

5. Alexander, F. A. D.: Amphetamine Sulfate for Acute Barbiturate Poisoning, *Correspondence, J. A. M. A.* **131**:1170 (Aug. 3) 1946.

The following physicians allowed us to use their clinical material: M. D. Allweiss, H. Arkin, L. Bloch, P. Daly, M. Gittleson, R. Grinker, M. Lev., E. Levine, J. Mehlman, L. Ohringer, S. Platt, R. Sternheimer and J. Reich. R. K. Richards, of Abbott Research Laboratories, North Chicago, Ill., advised us in the management of certain cases.

*Data on 11 Cases of Barbiturate Poisoning*

Case No.	Age	Sex	Drug and Amount Ingested	Condition on Admission	Lowest Blood Pressure	No. Hours Unconscious	Penicillin	Streptomycin	Aleptic Agents, Total Doses	Complications	Comment
1	56	M	Barbiturate and second sodium, amount unknown	Deep coma; absent reflexes	135-80	16			Picrotoxin, 198 mg.; desoxyephedrine hydrochloride, 40 mg.; amphetamine, 40 mg.		Mildly diabetic; responded well to therapy
2	22	F	Phenobarbital, amount unknown; second sodium 32 gr. (2.07 Gm.)?	Unconscious; only corneal and knee reflexes present	120-80	About 40			Picrotoxin, 373 mg.; desoxyephedrine hydrochloride, 60 mg.; caffeine anhydrous benzoate, 1.5 gr. (0.09 Gm.)	Arterial occlusion of brachial vein; patient slept on arm 12 to 15 hr. before admission	Unconscious 32 hr. before hospitalization
3	43	F	Tuinal, 15 gr. (0.97 Gm.)	Unconscious; facial grimaces with orbital pressure	140-70	About 18			Picrotoxin, 250 mg.; desoxyephedrine hydrochloride, 10 mg.		Few mild convulsions from picrotoxin
4	23	F	Phenobarbital, 45 gr. (2.91 Gm.)?	Deep coma; absent reflexes	110-60	64			Picrotoxin, 720 mg.; amphetamine, 320 mg.	Bronchopneumonia	Responded rapidly to picrotoxin (low convulsive threshold)
5	24	F	Phenobarbital, 100 gr. (6.48 Gm.)	Deep coma; absent reflexes	0-0	216			Picrotoxin, 5,439 mg.; desoxyephedrine hydrochloride, 680 mg.; metrazol, 143 cc.; caffeine and sodium benzoate, 25 Gm.	Shock 4th day of coma; bronchopneumonia; empyema in left lung	See discussion
6	48	F	Phenobarbital, 7 Gm.	Shock; required artificial respiration; absent reflex; deep coma	0-0	90			Picrotoxin, 1,017 mg.; amphetamine, 450 mg.; caffeine, 9 Gm.	Died	Radical mastectomy for carcinoma of breast 1 yr. before; multiple pulmonary and vertebral metastases noted at autopsy; bronchopneumonia
7	32	F	Second sodium, 90 gr. (5.82 Gm.)	Cyanosis; deep coma; absent reflex; required artificial respiration	70-90	About 78			Picrotoxin, 926 mg.; caffeine, 2 Gm.	Bronchopneumonia, fever (105 F.)	Developed foot drop; urine negative for heavy metal
8	67	F	Phenobarbital(?)	Comatose; gag reflex present	118-90	48			Picrotoxin, 558 mg.		
9	60	F	Second sodium, phenobarbital (?)	Comatose; all reflexes present	120-70	Unconscious 24 hr. prior to her admission			Picrotoxin, 225 mg.; desoxyephedrine hydrochloride, 120 mg.	Abscess developed on sacrum	Responded rapidly to picrotoxin (low convulsive threshold)
10	32	F	Alurate sodium (?)	Deep coma; corneal reflex present	80-?	35			Picrotoxin, 760 mg.; desoxyephedrine hydrochloride, 100 mg.	Numerous convulsions	.....
11	30	F	Phenobarbital, 150 gr. (9.72 Gm.)	Deep coma	60-30	135			Picrotoxin, 14,196 mg.; desoxyephedrine hydrochloride, 140 mg.; amphetamine, 1,950 mg.	Numerous convulsions; bronchopneumonia	See discussion

Note: Only patients 5 and 11 had both penicillin and streptomycin; all others just had penicillin.

120 systolic and 80 diastolic; all reflexes were absent, and there was no response to painful stimuli. Supportive therapy as outlined previously was instituted, and analeptic treatment was started at once. The patient was given picrotoxin every fifteen minutes intravenously, the highest individual dose being 15 mg. (5 cc.). During the nine days of unconsciousness, multiple complications occurred. On the fourth day in the hospital the blood pressure dropped suddenly and was unobtainable, but it was effectively restored to normal within two hours with the use of plasma and desoxyephedrine hydrochloride. A severe pneumonic infection occurred, with a localized area of dullness in the base of the left lung posteriorly. On a roentgenogram a bilateral process with a left pleural effusion was noticed, which on aspiration proved to be an encapsulated empyema. Thoracentesis and instillations of penicillin into the thoracic cavity caused remission of the ten day febrile course in forty-eight hours. This patient received both penicillin and streptomycin during the entire febrile period. Although she had numerous convulsions during the period of intensive therapy, no apparent residual effects were noted in several weeks of subsequent hospitalization. The patient received a total of 5,139 mg. of picrotoxin, a higher dose than any reported in the literature surveyed. In addition, she received 143 cc. of "metrazol," 689 mg. of desoxyephedrine hydrochloride and 25 Gm. of caffeine and sodium benzoate U.S.P.

CASE 11.—This patient, a 30 year old white woman, was hospitalized about five hours after having taken approximately 150 grains (9.72 Gm.) of phenobarbital. The initial response to 15 mg. of picrotoxin given intravenously was good, that is, twitching resulted. Within eight to ten hours, however, extreme deterioration occurred. Whereas corneal and gag reflexes were present on her admission, these could no longer be elicited, and respiratory depression had become pronounced. A test dose of 1 cc. "metrazol" administered intravenously along with the picrotoxin on her admission had evoked a brief convulsion; but now the patient was no longer stimulated by 3 cc. of "metrazol," which signified roughly the increasing depth of coma. Since the patient no longer responded to the orthodox therapy recommended, we felt that more radical doses must be administered. The usual 15 mg. dose was progressively increased to 45 mg. (15 cc.) every fifteen minutes. At this level we were once again able to obtain a preconvulsive state. Clinically, the patient showed early signs of improvement with the elevated dose; the blood pressure rose, and the respiratory exchange was improved. In the course of several hours this dose was reduced slowly to lower levels, with constant maintenance of an irritable state. The patient received more than 15 mg. of picrotoxin every fifteen minutes for more than one hundred and four hours. At the end of the fifth day of unconsciousness, the patient opened her eyes and responded to simple instructions. An attempt was made to stop all therapy, but within one hour the patient slipped back into coma, and vigorous therapy was again resumed. By the end of the next twenty-four hours the patient was talking and sipping fluids, but constant stimulation was required to maintain this state for another twelve hours. The fact that barbiturates were present in the urine on the eighth day after her return to consciousness explained the necessity for constant stimulation to prevent relapse. This case, like many others, was complicated by extensive bronchopneumonia. Penicillin and streptomycin were given from the beginning of therapy, in spite of which the patient's illness ran a stormy, febrile course. Aerosol penicillin was instituted once the patient was conscious to help stem the severe bronchopneumonia. During the period of unconsciousness, an acute gastric dilatation occurred, requiring Wangenstein suction for several days. The patient received 14,196 mg. of picrotoxin, and 1,950 mg. of amphetamine

were given concomitantly in doses of 10 to 30 mg. intravenously. To our knowledge, the total dose of picrotoxin is the highest recorded in current literature. At the end of two weeks the patient was no longer considered a medical problem and was transferred to the department of psychiatry.

#### COMMENTS AND CONCLUSIONS

Severe barbiturate poisoning may require much larger doses of picrotoxin than those usually recommended. It is our experience that no arbitrary dose exists in this regard. The amount of picrotoxin given must be varied according to the depth of coma, which can be judged not only by the amount of intoxicant ingested and the time elapsed before treatment is instituted, but also by the patient's response to the previous dose of picrotoxin. While a patient is comatose, there is no toxic dose of picrotoxin until a preconvulsive state is reached. The average dose administered during the acute phase was 15 mg. every fifteen minutes.

"Metrazol" is a valuable aid in the estimation of the depth of coma.

It should be emphasized that after the patient begins to respond to smaller and smaller doses of picrotoxin with preconvulsive twitchings, indicating an awakening of the lower brain centers, therapeutic stimulation of the cortex by amphetamine is indicated, since picrotoxin is not primarily a cortical stimulant. If all medication is stopped as soon as the patient begins to awaken, he will go back into coma, especially when barbital or phenobarbital has been ingested, since these drugs are excreted slowly. In 1 of our cases, phenobarbital was still being excreted in the urine five days after consciousness first returned.

• Maintenance of fluid balance, constant vigilance in keeping the air passages clear and, above all, immediate administration of antibiotic substances to help prevent pulmonary infection are necessary if the analeptic agents are to have a chance to reverse the intoxication. If these measures are not instituted, the patient may die before sufficient time has elapsed to allow neutralization of the intoxicants.

All 11 patients in this series received penicillin; bronchopneumonia developed in 4 of the patients while they received penicillin therapy. The 2 patients reported on in detail (cases 5 and 11) were given both streptomycin and penicillin; 1 patient (case 5) had a complicating encapsulated empyema which responded to local instillations of penicillin into the thoracic cavity. The other patient (case 11) recovered from bronchopneumonia only when aerosol penicillin was added to the usual parenteral administration of antibiotic drugs.

It is apparent that medical therapy is only the beginning of treatment, which should in all cases be continued by placing the patient in the hands of a psychiatrist.

# Progress In Internal Medicine

## ALLERGY

A Review of the Literature of 1946 and 1947

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IN THE two years that have elapsed since the review of the literature of 1944 and 1945 was presented<sup>1</sup> several advances in knowledge have been made.

The first is a dramatic advance. It concerns the antihistaminic drugs which late in 1945 were hailed as a possible panacea for allergic diseases of every kind. A large number of papers have described the many aspects of it. The second is more clinical and practical; it concerns the psychosomatic factors which are being recognized more and more in the cause of asthma. The third is the new development in the understanding of the pathologic aspects of asthma and kindred states and their relation to similar lesions produced by a similar mechanism in other diseases. Finally, the treatment of patients has been improved by the method of administering drugs directly to the nasal and bronchial mucosa in the form of a fine spray, or "aerosol."

It is to be noted that these forward steps have been taken not by the workers in allergy itself but by investigators in other fields. It is their work in pharmacology and pathology which finds application in allergy. Through their work, the concept of the causes of asthma has been widened materially, and through it the concept of allergic reactions as important factors in other diseases besides asthma, hay fever, urticaria and eczema has been advanced. The phrase "all is not allergy that wheezes" has found ample support.

In the last review I pointed out that the production of symptoms in allergic diseases required four distinct steps. First, the asthmatic state, the "X" factor, is essential, for it explains why hay fever, asthma or eczema develop in only certain persons. In persons with a "Y" factor arthritis might develop, or in a third group, with a "Z" factor, mucous colitis might develop, or perhaps migraine headaches or peptic ulcer.

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1. Rackemann, F. M.: Allergy: A Review of the Literature of 1944 and 1945, with Comments on Future Problems, *Arch. Int. Med.* **77**:700 (June) 1946; **78**:108 (July) 1946.

In each case the patient is "conditioned," so that when exciting causes and other factors come to him chronic disease of a certain type peculiar to his predisposition develop. It is interesting to observe that it is uncommon for more than one of these chronic disease groups to develop in a patient. The patients with asthma almost never have peptic ulcer.

Granted the asthmatic state in the background, the theory is that the second step has one of four different mechanisms, any one of which can release a histamine-like substance to constitute the third step, and this in turn can produce any one of a variety of symptoms as the fourth step. The typical mechanism of the second step is the antigen-antibody reaction of allergy, but there is reason to think that infectious processes can cause the same release of H substance. Intoxication by drugs, like the sulfonamide drugs, can do the same thing, and then, of greater interest, is the concept that depletion (a general lowering of the vitality, whether on a somatic or psychic basis) can also release H substance and produce the symptoms which together constitute clinical allergy.

The current literature, in the order of these four steps, may be considered in two parts: Part I includes the first three steps through the release of histamine. It is a complex process which involves the review of experimental evidence. Part II is more clinical: the review of recent advances in pathology, in diagnosis and in treatment.

## PART I. MECHANISM OF SYMPTOM PRODUCTION

### THE ASTHMATIC STATE

Ever since 1932, when Weiss, Robb and Ellis<sup>2</sup> first observed that the patient with asthma reacted to an intravenously administered dose of histamine differently than did the normal person, it has been recognized that the difference is basic. New papers confirm the observation. Curry<sup>3</sup> took repeated measurements of the vital capacity while injecting histamine intravenously in small amounts into patients with asthma and normal persons. Only in the former group did the figure fall. Later, Curry<sup>4</sup> compared the effect of methacholine chloride ("mecholyt chloride") (acetyl-beta-methylcholine) with histamine and observed it to be even more active in reducing the vital capacity. In normal persons neither

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2. Weiss, S.; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiovascular System, *Arch. Int. Med.* **49**:360 (March) 1932.

3. Curry, J. J.: The Action of Histamine on the Respiratory Tract in Normal and Asthmatic Subjects, *J. Clin. Investigation* **25**:785, 1946.

4. Curry, J. J.: Comparative Action of Acetyl-Beta-Methyl Choline and Histamine on the Respiratory Tract in Normal Patients with Hay Fever and Subjects with Bronchial Asthma, *J. Clin. Investigation* **26**:430, 1947.

histamine nor "mecholy chloride" produced any change in the vital capacity. Rose<sup>5</sup> also has worked with injections of histamine, observing that whereas peripheral vasodilatation (flushing) occurs in all subjects, whether allergic or not, asthma, urticaria or headache occurred only in those who were predisposed to these allergic manifestations.

The factor of one's constitution is as important as it is obscure. Resistance to the common cold, for example, has been shown by Sargent, Lombard and Sargent<sup>6</sup> to be rather stable. In a large boarding school each boy had the same number of colds, some more and some less than the average, but each year the same. Constitution is inherited, and now Stiles and Johnston<sup>7</sup> present another study of inheritance. In a family of 232 persons, asthma and hay fever occurred in 22.4 per cent, in contrast to the figure of about 7 per cent for the general population. The concept of a constitutional abnormality—of an "asthmatic state"—in certain susceptible persons is justified.

*The Theory of the Release of Histamine.*—That antigen-antibody reactions can release H substance is the heart and soul of allergy. The fact goes far to explain the precipitation of a typical group of symptoms by reactions set up by a wide variety of specific foreign substances. That much is clear. Can the same symptoms, dependent on the release of the same H substance, be precipitated by other mechanisms—infection, intoxication and especially depletion? It is the observation in patients in the clinic which indicates that these other factors must be important.

In a recent paper<sup>8</sup> I described a working classification of asthma. The patients in whom asthma begins before the age of 30 are usually allergic, and their asthma should be considered as dependent on allergy until proved otherwise. The methods of allergy appear to be adequate in diagnosis and treatment. A study of the older age group is more interesting; when asthma begins after the age of 40, it is my opinion that the cause should be considered as something other than allergy until proved otherwise. When in a young person asthma becomes severe, so that the patient must be admitted to the hospital, great improvement frequently follows within three days, the patient probably having escaped from a dust which was causing trouble at home. In an older

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5. Rose, B.: Role of Histamine in Anaphylaxis and Allergy, *Am. J. Med.* 3:545, 1947.

6. Sargent, F.; Lombard, O. M., and Sargent, V. W.: Further Studies on Stability of Resistance to the Common Cold, *Am. J. Hyg.* 45:29, 1947.

7. Stiles, K. A., and Johnston, E. J.: Study of Inheritance of Respiratory Allergies, *J. Allergy* 17:11, 1946.

8. Rackemann, F. M.: Working Classification of Asthma, *Am. J. Med.* 3:601, 1947.

person, however, the asthma continues even in the new and clean environment, the cause being something which the patient carries with him. The asthma is "intrinsic."

There are various theories to explain this "intrinsic" asthma. In his new book Cooke<sup>9</sup> describes "infective" asthma. He expresses the belief that new colds are a satisfactory explanation for the kind of asthma which occurs in children and young adults at long intervals and in short seizures; he agrees with me that for this group the term "asthmatic bronchitis" is satisfactory. Whether the more persistent asthma which begins rather suddenly in men and women past the age of 40 can be attributed to a form of allergy to the bacteria involved in the focus of infection, or perhaps in the diffuse infection of the sinuses and bronchi, is obviously the important question. The difficulty about demonstrating this allergy through cutaneous tests has made it difficult to explain the process of this basis with real finality.

In a more recent paper Cooke<sup>10</sup> places his "infective" asthma under the general heading of delayed inflammatory reactions, implying that reactions to cutaneous tests of the immediate urticarial wheal and erythema variety need not be expected in this group. When cutaneous tests with intradermal injections of whole organism vaccines or filtrates of broth cultures are made inflammatory reactions are often observed in twenty-four hours. Rarely does one see an immediate wheal and erythema reaction after administration of vaccines. Cutaneous tests with the carbohydrate fractions should be made, for, as Francis and Abernathy<sup>11</sup> showed long ago, it is the soluble specific substance contained in the carbohydrate which gives the immediate reaction. There are difficulties with both types of tests. Delayed inflammatory reactions of the tuberculin type point, like tuberculin itself, to the past history of the patient as much as to his present illness. One needs only to consider the fallacy that the demonstration of a positive reaction to tuberculin could prove that the asthma is tuberculous in origin.

Tests with bacterial carbohydrates may become more interesting, but the high degree of specificity among bacterial species imposes considerable practical difficulties. The test requires carefully made cultures, and it requires a rather complex technic for isolating the carbohydrate fraction from the various bacteria isolated. The problem is not easy, but it should be investigated.

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9. Cooke, R. A., and others: *Infective Asthma with Pharmacopeia*, in Cooke, R. A.: *Allergy in Theory and Practice*, Philadelphia, W. B. Saunders Company, 1947, chap. 7, p. 130.

10. Cooke, R. A.: *Immunology of Allergic Disease*, *Am. J. Med.* 3:523, 1947.

11. Francis, T., Jr., and Abernathy, J. J.: *Cutaneous Reactions in Pneumonia to a Somatic "C" Polysaccharids of Pneumococcus*, read before the Society for Clinical Investigation, May 1934.



Intoxication due to drugs, as a mechanism for the release of H substance, will be discussed under allergy due to drugs. No direct observations have been made, and the concept depends almost entirely on clinical evidence. This, however, demonstrates that drugs can cause allergic symptoms as well as can pollens, animal danders or even foods.

Depletion has been described by me<sup>12</sup> as a cause of asthma. The conception of Selye,<sup>13</sup> with his discussion of the general adaptation syndrome, was noted in a previous review. His thesis is that stress and strain, whether of physical, infectious or emotional origin, can give rise to a number of changes in the body and that asthma may be one of these. This concept is in agreement with my own idea<sup>12</sup> that depletion may be in itself an adequate cause of asthma. In patients who are conditioned, as it were, by having the asthmatic state, depletion, or, perhaps better, stress and strain of various kinds, can produce the same symptoms which follow the ordinary antigen-antibody reaction of allergy. (The conditioning is important.) Since in many cases the depletion comes first and the asthma follows, one has to think of a cause and effect relationship. The clinical picture includes loss of weight, strength and courage, but it also includes rather typical exhaustion, which has been termed "allergic toxemia." One observes a low temperature, low blood pressure, rapid pulse rate and low white cell count. Clinical observation indicates that the factor of depletion is real.

Depletion may be somatic and may develop because of malnutrition or perhaps because of some more definite disturbance, like abscessed teeth or a focal infection in the sinuses, gallbladder or elsewhere, but depletion can also be of psychic origin, and there is increasing clinical evidence to support that theory. Henderson<sup>14</sup> writes about the psychogenic factors in bronchial asthma. Brown and Goitein<sup>15</sup> and Metzger<sup>16</sup> lay stress on the emotional aspects of their patients with asthma, and Gliebe and Kerr<sup>17</sup> present a number of interesting histories of patients, each of whom was relieved simply by appropriate reeducation. Miller, and

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12. Rackemann, F. M.: Depletion in Asthma, *Tr. Am. Clin. & Climatol. A.* **58:71**, 1946.

13. Selye, H.: The General Adaptation Syndrome and the Disease of Adaptation, *J. Allergy* **17:231**, 289 and 358, 1946.

14. Henderson, A. T.: Psychogenic Factors in Bronchial Asthma, *Canad. M. A. J.* **106:55**, 1946.

15. Brown, E. A., and Goitein, P. L.: The Meaning of Asthma, *Psychoanalyt. Rev.* **31:299**, 1944.

16. Metzger, F. C.: Emotions in the Allergic Individual, *Am. J. Psychol.* **103:697**, 1947.

17. Gliebe, P. A., and Kerr, W. J.: Recognition of Emotional Factors in Allergic Manifestations, *Am. J. Med.* **3:607**, 1947.

Baruch<sup>18</sup> told stories of children who were frustrated in various ways and learned to use their asthma as an escape mechanism. In discussion of this paper, Dr. J. H. Mitchell pointed out that in the young group male and female patients are about equal in number, but in the older group women outnumber the men 2 to 1. In other papers one reads of actual cases or of the suggestion that nervous factors were predominant in the particular problem. I am learning to pay close attention to the emotional aspects as well as to the physical environment of the patient.

What objective evidence is there to support this concept of depletion? Wolff<sup>19</sup> studied the mucous membrane of the stomach in a patient who came to him with gastric stoma, like that of Alexis St. Martin, the patient of William Beaumont. When this boy was frightened decided vasoconstriction, both of the gastric membrane and of the nose, became apparent, and then when fear turned to rage the opposite took place—redness and swelling developed at once. Fowler<sup>20</sup> described a soldier whose nose became pale and boggy as long as he was in the army, but on discharge all his symptoms cleared away.

Frabricant<sup>21</sup> describes the rapid shift in the  $p_{\text{H}}$  of the nasal secretions, from slightly acid to alkaline, which fright could induce in 3 of his patients.

Brown and Venning<sup>22</sup> show that emotional disturbances, as well as burns, infections, fractures and operations, can result in a rapid increase in the urinary excretion of the glucogenic corticoid hormones, thus indicating an increase of the activity of the adrenal cortex. Forbes and her co-workers<sup>22a</sup> have observed that under conditions of stress the 17-ketosteroids are increased at first and fall to subnormal values later. Brown<sup>23</sup> submits the report of a man aged 34, with many allergic symptoms, who was relieved by taking diphenhydramine hydrochloride ("benadryl hydrochloride") 50 mg. twice a day. With the medication

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18. Miller, H., and Baruch, D. W.: Group and Individual Psychotherapy as an Adjunct in the Diagnosis and Treatment of Allergy, read before the American Academy of Allergy, New York, Nov. 25, 1946, unpublished data.

19. Wolff, H. A.: Life Situations, Emotions and Nasal Functions: A Report on Research, read before the American Society for Research in Psychosomatic Problems, New York, Feb. 15, 1946.

20. Fowler, E. P., Jr.: A Nose and Throat Viewpoint, read before the American Society for Research in Psychosomatic Problems, New York, Feb. 15, 1946.

21. Fabricant, N. D.: Effect of Emotions on the Hydrogen Ion Concentration of Nasal Secretion in Situ, with Comment on Terminology of Nasal Hydrogen Ion Concentration Measurement, *Arch. Otolaryng.* **43**:402 (April) 1946.

22. Browne, J. S. L., and Venning, L. H.: The Response of the Adrenal Cortex to Disease and Trauma, *Tr. A. Am. Physicians* **60**:16, 1947.

22a. Forbes, A. P.; Donaldson, E. C.; Reifenshtein, E., Jr., and Albright, F.: The Effect of Trauma and Disease on the Urinary 17-Ketosteroid Excretion in Man, *J. Clin. Endocrinol.* **7**:264 (April) 1947.

23. Brown, W. T.: The Probable Role of Histamine in Some Emotionally Precipitated Allergic Conditions, *Yale J. Biol. & Med.* **19**:63, 1946.

his emotions did not cause asthma any more. It is obvious that the authors of these papers agree with Dr. Cannon,<sup>24</sup> who originally demonstrated that emotion can produce physiologic changes.

An argument against the idea that depletion is concerned with antigen-antibody reactions of any kind occurs in a paper by Vezina.<sup>25</sup> He talks about "fasting immunity," or "malnutrition immunity," pointing out that neither prisoners of war nor poorly nourished infants are particularly subject to infection. He cites Sprunt<sup>26</sup> as well as Foster and his co-workers,<sup>27</sup> who observed that vaccines and viruses do not survive well in animals whose cells have been deprived of certain important nutrients. This paper encourages the suggestion that depletion, which clinically is a satisfactory explanation in certain cases, depends more on a physiologic disturbance of hormones, or other factors, than on any influence on immune processes, whether concerned with allergy to dusts or foods or with the reactions to infections.

None of this previous work deals with the actual release of H substance by infection or by stress and strain. So far one can only assume that since depletion, as well as infection, intoxication and allergy itself, can cause asthma and kindred allergic symptoms, the mechanism is by way of the release of H substance. Further study of histamine itself and, especially, of the new antihistaminic drugs will help to clarify the problems. As said in the opening paragraph, it is the discovery and distribution of the antihistaminic drugs which constitute the dramatic advance since 1945.

*Histamine Release.*—A number of good reviews have been written on the subject of histamine and the antihistaminic drugs. In 1943, Dragstedt<sup>28</sup> wrote "The Significance of Histamine in Anaphylaxis and Allergy." Rocha e Silva<sup>29</sup> in 1944 published "Recent Advances in the Histamine Problem." He emphasized the observation that other mechanisms besides the antigen-antibody reaction could release hista-

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24. Cannon, W. B.: *The Wisdom of the Body*, New York, W. W. Norton & Company, Inc., 1932.

25. Vezina, N.: *L'immunité par la sous-alimentation*, Union méd. du Canada **76**:971, 1947.

26. Sprunt, D. H.: Effect of Undernourishment on Susceptibility of Rabbit to Infection with Vaccinia, *J. Exper. Med.* **75**:297, 1942.

27. Foster, C.; Jones, J. H.; Henle, W., and Dorfman, F.: The Comparative Effects of Vitamin B<sub>1</sub> Deficiency and Restriction of Food Intake on the Response of Mice to the Lansing Strain of Poliomyelitis Virus, as Determined by the Paired Feeding Technique, *J. Exper. Med.* **80**:257, 1944.

28. Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis and Allergy, *Quart. Bull., Northwestern Univ. M. School* **17**:102, 1943; The Significance of Histamine in Anaphylaxis, *J. Allergy* **16**:69, 1945.

29. Rocha e Silva, M.: Recent Advances Concerning the Histamine Problem, *J. Allergy* **15**:399, 1944; *Histamine with Anaphylaxis*, Sao Paulo, Brazil, Grafica e Editores Edigraf Ltd., 1946.

mine. He demonstrated that animal poisons, like snake venom and bee venom, can release histamine by an action which runs rather parallel to the hemolytic activity of these substances. Trypsin also releases histamine from cells, especially in the liver, and treatment with trypsin results in an increase of histamine in the blood plasma. Arginine and histidine, on the other hand, counteract the histamine effect. These amino acids contain an imino- group ( $\text{NH}$ ) which anchors the histamine to the tissues by a peptid linkage. Histamine which is bound to the cell is rather inactive. In the test tube the peptid linkage is easily broken down by acid hydrolysis; in the body it may be broken by proteolytic enzyme, the so-called intracellular cathepsin of the tissue fluids. The reason that bee venom is so poisonous is that it, too, can break the linkage and allow bound histamine to become free plasma histamine. Peptone and specific antigens release histamine by a similar chemical mechanism. One should note that the clinical symptoms of all these processes, whether from an antigen-antibody reaction, bee sting or injection of peptone or trypsin, are the same. As Dragstedt says, the histamine theory is at least plausible.

More recently, Rose<sup>5</sup> of Montreal has presented a useful and comprehensive discussion of this problem. He lays stress on the ready shift between bound histamine and free histamine.

The experiment of Katz<sup>30</sup> is important. In 1940 Katz showed that when horse serum was added in vitro to the blood of a rabbit sensitized with horse serum the amount of histamine in the cell-free plasma increased greatly. Rose and Browne<sup>31</sup> confirmed this experiment. When egg albumin was added to the blood of an egg-sensitive rabbit, the amount of histamine in the plasma increased to ten times the amount obtained when the same blood was mixed with isotonic solution of sodium chloride and five times the amount when it was mixed with horse serum. It is the interchange which explains the irregularity in the measurements of histamine in the circulating blood. The method of assay requires heating of the specimen in the presence of acid, and this treatment is enough to break the linkage and convert all the histamine present into free unbound histamine. The method, therefore, indicates the total histamine and not merely the free histamine in the sample. Rocha e Silva<sup>29</sup> bound histamine to amino acids artificially and then observed that, whereas the combination had no physiologic action,

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30. Katz, G.: The Role of Blood Cells in the Anaphylactic Histamine Release, *J. Pharmacol. & Exper. Therap.* **72**:22, 1941. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, *J. A. M. A.* **117**:1782 (Nov. 22) 1941.

31. Rose, B., and Browne, J. S. L.: Studies on the Release of Histamine from the Blood Cells of the Rabbit by the Addition of Horse Serum or Egg Albumin in Vitro, *J. Immunol.* **41**:403, 1941.

31a. Rose, B.: Personal communication to the author.

the assay for histamine which destroyed the linkage in the process showed the original amount still present. If this shift can occur from blood to tissue cells as well as from plasma to blood cells and back again, it is not surprising that the amount of histamine seen in a given specimen of blood does not run parallel to the severity of allergic symptoms. One gets the impression that histamine can change from the free to the bound state and back again rather readily. Rose points out, however, that, whereas the evidence of transfer from the bound to the free state is ample, there is not yet any direct method for showing the reverse, namely, a shift from the free to the bound state. In his review, Rose<sup>5</sup> recalls that Code<sup>32</sup> showed that in anaphylaxis in dogs there is in the early stages a rapid release of free histamine, but as the process continues death may occur at a time when the amount of histamine in the blood has become normal again. The last two sentences of Rose's paper<sup>5</sup> are quoted:

It seems probable that small amounts of histamine may be continually released in some cases of allergy producing local symptoms, and rapidly removed by means of kidney or intestine as evidenced by the increased histamine content of urine and feces under these conditions. A marked increase in the total blood histamine without alteration of the plasma histamine is completely compatible with absence of symptoms.

This change in the state of histamine from being bound to cells to being free in the plasma makes it difficult to analyze the process in allergy. So far the literature contains few references to the comparative measurements of free histamine in the plasma with bound histamine in the blood cells in patients. It appears to me that further study of this aspect might be fruitful. Meantime, other mechanisms are undoubtedly involved, and it is the antihistaminic drugs and the study of their pharmacologic aspects which have provided the best evidence that the complete explanation does not lie in histamine itself. In the next section are brought out the several discrepancies between the effects of these drugs in experiments with histamine and their effects in experiments involving antigen-antibody reactions.

*Antihistaminic Drugs.*—There are three ways in which the effect of histamine can be inhibited. First, it has been said that histamine could be destroyed by a ferment histaminase. In experiments with animals the ferment was often effective, but in human beings the results of treatment with histaminase have been disappointing. Second, attempts to increase the natural resistance against histamine have been made, sometimes by repeated injections of histamine itself, sometimes by using the histamine azoprotein called "hapamine" (a chemical combination of histamine and despeciated horse serum globulin), which Fell,

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32. Code, C. F.: The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, *Am. J. Physiol.* **127**:78, 1939.

Rodney and Marshall<sup>33</sup> first produced in 1943. In both cases, however, the results have been disappointing. Neither with histamine nor with "hapamine" has the treatment been effective. The third method is more recent, and results are much more dramatic. A series of new compounds, referred to as antihistaminic drugs, has been developed. They can neutralize histamine in the test tube. These drugs include certain aromatic derivatives of aminoethanol and ethylenediamine, as well as benzohydril ethers of beta-dimethylaminoethanol. All are closely related, and all are able to antagonize histamine without eliciting pharmacologic responses. They do not, like epinephrine, produce an opposing effect. The literature on these drugs has been reviewed in two papers by Feinberg.<sup>34</sup> The pharmacologic aspects of antihistamine compounds have been reviewed in detail by Loew.<sup>35</sup> The important points are as follows:

In 1933 Fournau and Bovet<sup>36</sup> developed their compound "929 F" (thyroxyethyldiethylamine), and in 1937 Staub and Bovet<sup>37</sup> described its antihistaminic properties. It protected guinea pigs against two lethal doses of histamine. Twelve years later the new drug tripelennamine hydrochloride ("pyribenzamine hydrochloride") was observed to be from one thousand to ten thousand times as active against histamine as was "929 F." "Benadryl" and "pyribenzamine" are the two drugs which are available for clinical use today. "Antergan" (dimethylamino-ethyl benzylaniline) and "neoantergan" (N-p-methoxybenzyl-N'-dimethyl-aminoethyl  $\alpha$  aminopyridine) are less well known. New and even better preparations are being manufactured. "Benadryl" (beta-dimethylamino-ethyl benzohydril ether hydrochloride) was developed by Loew and his associates<sup>38</sup> in the laboratories of Parke, Davis & Company in February 1945. "Pyribenzamine" (N pyridyl-N benzyl-N-dimethylethylenedia-

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33. Fell, N.; Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes: Synthesis and Immunologic Investigation; Histamine-Azoprotein, *J. Immunol.* **47**:237, 1943.

34. Feinberg, S. M.: Histamine and Antihistaminic Agents: Their Experimental and Therapeutic Status, *J. A. M. A.* **132**:702 (Nov. 23) 1946; The Antihistaminic Drugs: Pharmacology and Therapeutic Effects, *Am. J. Med.* **3**:560, 1947.

35. Loew, E. R.: Pharmacology of Antihistaminic Compounds, *Physiol. Rev.* **27**:542, 1947.

36. Fournau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau dérivé du dioxane, *Arch. internat. de pharmacodyn. et de thérap.* **46**:178, 1933.

37. Staub, A. M., and Bovet, D.: Action de la thymoxyéthyl-diéthylamine (929 F.) et des éthers phénoliques sur le choc anaphylactique du cobaye, *Compt. rend. Soc. de biol.* **125**:818, 1937.

38. Loew, E.; Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, *J. Pharmacol. & Exper. Therap.* **83**:120, 1945.

mine) was developed by Mayer, Hutterer and Scholz<sup>39</sup> in the laboratories of the Ciba Pharmaceutical Products, Inc., in July 1945.

"Antergan" (N phenyl-N benzyl-N-dimethylethylenediamine) was developed by Halpern<sup>40</sup> from compounds synthesized by Mosnier in the laboratories of the Rhone-Poulenc Society in France in 1942.

"Neoantergan" (N-p-methoxybenzyl-N-dimethylaminoethyl  $\alpha$  aminopyridine) appeared two years later, being made by Bovet and associates<sup>41</sup> in France. (One observes that the French did this important work despite the war and, also, that the French, in their laboratories, were about three years ahead of us.) These four formulas are much alike, and their pharmacologic actions are rather similar.

The clinical results of the use of "benadryl" and "pyribenzamine" as reported in the literature are so numerous that it is best to review them as a series of tables. To make the figures as comparable as possible, I have added the figures for "excellent" results to the figures for "good" results.

TABLE 1.—Results of Treatment for Hay Fever

Author	No. Cases	Results		Poor No. of Cases
		Excellent and Good		
		No. of Cases	Percentage	No. of Cases
TREATMENT WITH H "BENADRYL"				
Friedlaender (Footnote 53).....	19			19
Logan (Footnote 44).....	12	9	75	3
McElin and Horton (Footnote 45).....	22	21	94	1
Koelsche, G. A.; Prickman, L. E., and Carryer, H. M. J. <i>Allergy</i> 17:151, 1946; <i>Proc. Staff Meet.,</i> <i>Mayo Clin.</i> 20:432, 1945.....	52	39	75	13
Waldrott (Footnote 48).....	31	23	74	8
Levin (Footnote 52).....	78	46	59	32
McGavack, Elias and Boyd (Footnote 47).....	8	6	75	2
Eyermann, C. H.: <i>J. Allergy</i> 17:210, 1946.....	52	47	90	5
Friedlaender and Feinberg (Footnote 54).....	19	2	10	17
Wagner (Footnote 49).....	38	24	63	14
Loveless, M. H., and Brown, H.: <i>New England J.</i> <i>Med.</i> 237:501, 1947.....	38	31	81	7
Bernstein, Rose and Feinberg (Footnote 42).....	54	28	52	26
Blumenthal, L. S., and Rosenberg, M. A.: <i>J.A.</i> <i>M.A.</i> 135:20 (Sept. 6) 1947.....	23	15	65	8
Total for "benadryl".....	446	291	66	155 (34%)
TREATMENT WITH "PYRIBENZAMINE"				
American Academy of Allergy (Footnote 50).....	104	56	54	48
Arbesman, Koepf and Lenzner (Footnote 51).....	140	119	85	21
Loveless, M. H., and Brown, H.: <i>New England</i> <i>J. Med.</i> 237:501, 1947.....	60	51	85	9
Bernstein, Rose and Feinberg (Footnote 42).....	254	208	82	46
Henderson and Rose (Footnote 43).....	61	47	77	14
Total for "pyribenzamine".....	619	481	77	138 (22%)

39. Mayer, R. L.; Hutterer, C. P., and Scholz, C. R.: Antihistaminic and Anti-anaphylactic Activity of Some  $\alpha$ -Pyridino-Ethylenediamines, *Science* 102:93, 1945.

40. Halpern, B. N.: Etude expérimentale des antihistaminiques de synthèse: Essais de chimiothérapie des états allergiques, *J. de méd. de Lyon* 23:409, 1942.

41. Bovet, D.; Horclois, R., and Walthert, F.: Propriétés antihistaminiques de la n-p-méthoxybenzyl-n-diméthylaminoéthyl  $\alpha$  amino-pyridine, *Compt. rend. Soc. de biol.* 138:99, 1944.

In hay fever (table 1) the total results with "benadryl" were good, and often excellent, in 66 per cent of the cases, but the figures vary and many of the groups were small. With "pyribenzamine" the results were better—77 per cent good results.

In chronic vasomotor rhinitis (table 2) the results of treatment with "benadryl" have been reported by Bernstein, Rose and Feinberg,<sup>42</sup> by

TABLE 2.—Results of Treatment for Vasomotor Rhinitis with "Benadryl" and "Pyribenzamine"

Author	No. of Cases	Results			
		Excellent and Good		Poor	
		No. of Cases	Percentage	No. of Cases	Percentage
		TREAT	MENT WITH	"BENADRYL"	
Bernstein, Rose and Feinberg (Footnote 42).	40	7	17	33	82
Henderson and Rose (Footnote 43). . . . .	21	13	62	8	38
Eight Authors (referred to in text) . . . . .	104	64	61	40	38
Total for "benadryl" . . . . .	165	84	51	81	49
TREATMENT WITH "PYRIBENZAMINE"					
American Academy of Allergy (Footnote 50).	277	164	59	113	41
Arbesman, Koepf and Lenzner (Footnote 51)	138	100	72	38	27
Bernstein, Rose and Feinberg (Footnote 42).	130	83	64	47	36
Total for "pyribenzamine" . . . . .	545	347	63	198	36

Henderson and Rose<sup>43</sup> and by eight other authors including Logan<sup>44</sup> (2 cases, McElin and Horton<sup>45</sup> (8 cases), Williams<sup>46</sup> (12 cases), McGavack, Elias and Boyd<sup>47</sup> (11 cases), Waldbott<sup>48</sup> (23 cases) and Wagner<sup>49</sup> (30 cases). In 165 patients treated with "benadryl," the results were excellent and good in 51 per cent. With "pyribenzamine" the members of the American Academy of Allergy<sup>50</sup> reported good results in 59 per cent of 277 cases. Arbesman and his associates<sup>51</sup> obtained good results in 100 out of 138 cases, or 72 per cent, and the figures of Bernstein and his associates<sup>42</sup> fall between. The total figure with "pyribenzamine" was better than with "benadryl." It is interesting that in 35 cases of what Arbesman called "intrinsic nonseasonal rhinitis" the results with "pyribenzamine" were good in only 48 per cent.

42. Bernstein, T. B.; Rose, J. M., and Feinberg, S. M.: New Antihistaminic Drugs (Benadryl, Pyribenzamine, and Neoantergan) in Hay Fever and Other Allergic Conditions, Illinois M. J. **92**:8, 1947.

43. Henderson, A. T., and Rose, B.: Pyribenzamine (N-Pyridyl, N-Benzyl, Dimethyl-Ethylenediaminehydrochloride) in the Treatment of Allergy, Canad. M. A. J. **57**:136, 1947.

44. Logan, G. B.: The Use of Benadryl in Allergic Diseases of Childhood, Proc. Staff Meet., Mayo Clin. **20**:436, 1945.

45. McElin, T. W., and Horton, B. T.: Clinical Observations on the Use of Benadryl; A New Antihistaminic Substance, Proc. Staff Meet., Mayo Clin. **20**:417, 1945.

(Footnotes continued on next page)



Table 3 shows the results in asthma. In the total number, the results with "benadryl" were excellent and good in 42 per cent. Here the combined results with "benadryl" are somewhat better than the results with "pyribenzamine," but treatment with neither drug is really good in asthma. Waldbott<sup>48</sup> and Wagner<sup>49</sup> distinguish between seasonal asthma.

TABLE 3.—Results of Treatment for Asthma

Author	No. of Cases	Results		
		Excellent and Good		Poor
		No. of Cases	Percentage	No. of Cases
		TREATMENT WITH	"BENADRYL"	
Friedlaender (Footnote 53).....	9			9
Eyermann, C. H.: J. Allergy 17:210, 1946.....	16	6	38	10
Friedlaender and Feinberg (Footnote 54).....	16			16
Koelsche, G. A.; Prickman, L. E., and Carryer, H. M.: J. Allergy 17:151, 1946; Proc. Staff Meet., Mayo Clin. 20:432, 1945.....	12	4	33	8
Waldbott (Footnote 48).....				
Perennial bronchial asthma.....	48	24	50	24
Seasonal bronchial asthma.....	30	14	49	16
Levin (Footnote 52).....	37	57	65	30
McGavack, Elias and Boyd (Footnote 47).....	36	30	83	6
Wagner (Footnote 49).....				
Seasonal asthma.....	20	8	40	12
Intrinsic asthma.....	42	10	24	32
Fuchs, A. M.; Schulman, P. M., and McGavack, T. H.: North Carolina M. J. 7:141, 1946.....	30	7	23	23
Bernstein, Rose and Feinberg (Footnote 42).....	50	6	12	44
Total for "benadryl".....	396	166	42	230 (58%)

TREATMENT WITH "PYRIBENZAMINE"				
American Academy of Allergy (Footnote 50).....	222	70	31	152
Arbesman, Koepf and Lenzner (Footnote 51).....				
Grasses.....	12	6	50	6
Extrinsic (other than pollens).....	62	28	45	34
Bernstein, Rose and Feinberg (Footnote 42).....	121	33	28	88
Total for "pyribenzamine".....	417	137	33	280 (67%)

due presumably to pollen and therefore allergic, and perennial asthma, due to other causes. Wagner had much better results in the allergic extrinsic group. In Waldbott's two groups, however, the results were the same. In this table one observes that Levin<sup>52</sup> obtained good results

46. Williams, H. L.: Use of Benadryl in the Syndrome of Physical Allergy of the Head: A Preliminary Report, Proc. Staff Meet., Mayo Clin. 20:434, 1945. (Benadryl): Its Use in Allergic Diseases, J. Allergy 17:145, 1946.

47. McGavack, T. H.; Elias, H., and Boyd, L. J.: Some Pharmacological and Clinical Experiences with Dimethylaminoethyl Benzyhydriyl Ether Hydrochloride (Benadryl), Am. J. M. Sc. 213:418, 1947.

48. Waldbott, G. L.: Clinical Results with Benadryl, J. Allergy 17:142, 1946.

49. Wagner, H. C.: The Use of the New Antihistaminic Substances in the Treatment of Allergic Disorders, M. Clin. North America 31:43, 1947.

50. A Report of the Clinical Studies on the Use of Pyribenzamine in Allergic Diseases, the Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy, J. Allergy 17:325, 1946.

51. Arbesman, C. E.; Koepf, G. F., and Lenzner, A. R.: Clinical Studies with N'Pyridyl, N'Benzyl, Dimethylethylenediamine Monohydrochloride (Pyribenzamine), J. Allergy 17:275, 1946.

in 65 per cent of 87 cases, whereas neither Friedlaender<sup>53</sup> nor Friedlaender and Feinberg<sup>54</sup> observed any benefit from "benadryl" in the patients treated by them.

Urticaria appears to be the disease most amenable to treatment with antihistaminic drugs. Table 4 shows good results in 84 per cent of 334 patients treated with "benadryl" and in 79 per cent of 409 patients treated with "pyribenzamine." According both to Friedlaender and Feinberg,<sup>54</sup> who used "benadryl," and to Arbesman,<sup>51</sup> who used "pyribenzamine," the results were better in acute than in chronic urticaria. The members of the American Academy of Allergy, however, did not observe much difference.

TABLE 4.—Results of Treatment for Urticaria

Author	No. of Cases	Results		
		Excellent and Good		Poor
		No. of Cases	Percentage	No. of Cases
TREATMENT WITH "BENADRYL"				
Barefoot, S. W.; Riley, K. A., and Kuhn, B. H.: Am. J. Med. 3:309, 1947.....	19	16	84	3
Curtis, A. C., and Owens, B. B.: Arch. Dermat. & Syph. 52:239 (Oct.) 1945.....	18	14	177	4
Friedlaender (Footnote 53).....	12	12	00	
Various Authors.....	19	17	89	2
O'Leary, P. A., and Farber, E. M.: Proc. Staff Meet., Mayo Clin. 20:429, 1945.....	50	46	92	4
Eycrmann, C. H.: J. Allergy 17:210, 1946.....	14	13	95	1
Friedlaender and Feinberg (Footnote 54)				
Acute urticaria.....	16	14	87	2
Chronic urticaria.....	14	10	71	4
Waldbott (Footnote 48).....	20	16	80	4
Levin (Footnote 52).....	11	8	72	3
McGavack, Elias and Boyd (Footnote 47).....	36	33	92	3
Wagner (Footnote 49).....	46	34	74	12
Bernstein, Rose and Feinberg (Footnote 42).....	30	24	80	6
Blumenthal, L. S., and Rosenberg, M. A.: J.A. M.A. 135:20 (Sept. 6) 1947.....	29	24	82	5
Total for "benadryl".....	334	281	84	53 (16%)
TREATMENT WITH "PYRIBENZAMINE"				
American Academy of Allergy (Footnote 50)				
Acute urticaria.....	121	94	77	27
Chronic urticaria.....	97	76	78	21
Arbesman, Kocpf and Lenzner, (Footnote 51)				
Acute urticaria.....	47	44	93	3
Chronic urticaria.....	107	84	78	23
Bernstein, Rose and Feinberg (Footnote 42).....	37	28	78	9
Total for "pyribenzamine".....	409	326	79	83 (20%)

52. Levin, S. J.:  $\beta$ -Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl): Its Use in Allergic Diseases, J. Allergy 17:145, 1946.

53. Friedlaender, A. S.: The Use of a Histamine Antagonist, Beta-Dimethylaminethyl Benzhydryl Ether Hydrochloride in Allergic Disease, Am. J. M. Sc. 212:185, 1946.

54. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: III. The Effect of Oral and Local Use of  $\beta$ -Dimethylaminoethyl Benzhydryl Ether Hydrochloride on the Whealing Due to Histamine Antigen-Antibody Reactions, and Other Whealing Mechanisms; Therapeutic Results in Allergic Manifestation, J. Allergy 17:129, 1946.

54a. Through error, footnote numbers 55 to 63 were allowed for references which have been incorporated in table 4.

*Summary of Clinical Results.*—Taken together (table 5), the figures available so far indicate that “pyribenzamine,” with good results in 64 per cent of nearly 2,000 cases, is a little more effective than “benadryl,” with good results in only 61 per cent of 1,341 cases. A paper by Rose and his co-workers<sup>63</sup> from Feinberg’s laboratory shows that in guinea pig anaphylaxis, “benadryl” gives greater protection against shock than does “pyribenzamine.” In an interesting work on asthma experimentally produced in human beings by histamine aerosol, Curry<sup>64</sup> observed that “benadryl” given intravenously produced remarkably rapid protection against histamine, whereas “pyribenzamine” given by mouth produced a much slower protective effect. He recognized that the two drugs were not tested by the same method. In a recent paper, Loveless<sup>65</sup> has also made a comparative study of the literature on the clinical effects of “benadryl” and “pyribenzamine.” Her report gives many details omitted here, but her gross figures are comparable. More comparative studies on the clinical effects of these drugs are needed. The few comparative observations which have been made in the laboratory will be noted later.

Untoward Effects of the Antihistaminic Drugs. These are reviewed in the paper by Loveless. Sedation, or drowsiness, observed in 43 per cent of the patients treated with “benadryl,” occurred after administration of “pyribenzamine” in only 8.5 per cent. Gastrointestinal disturbances

TABLE 5.—*Summary of Results*

	Results with “Benadryl”			Results with “Pyribenzamine”		
	Total No. of Patients Treated	Good Results		Total No. of Patients Treated	Good Results	
		No. of Patients	Percentage		No. of Patients	Percentage
Hay Fever.....	446	291	65	619	481	77
Vasomotor rhinitis .....	165	94	51	545	347	63
Asthma.....	396	166	42	417	137	33
Urticaria.....	334	281	84	409	326	79
Total.....	1,341	822	61	1,990	1,291	64

63. Rose, J. M.; Feinberg, A. R.; Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: VII. Comparative Antianaphylactic Activity of Some New Antihistaminic Drugs; *J. Allergy* **18**:149, 1947.

64. Curry, J. J.: The Effect of Antihistamine Substances and Other Drugs on Histamine Bronchoconstriction in Asthmatic Subjects, *J. Clin. Investigation* **25**: 792, 1946.

65. Loveless, M. H.: Therapeutic and Side Effects of Pyribenzamine and Benadryl: Comparative Study Based upon a Survey on Twenty-Six Clinical Reports in the Literature, *Am. J. Med.* **3**:296, 1947.

occurred equally in the two series in about 8 per cent of the cases. Excitement, "jitters," insomnia and palpitation occurred in 10 per cent of the patients treated with "benadryl," but in only 3 per cent of the patients treated with "pyribenzamine." Dizziness was observed in 7 per cent after treatment with "benadryl" and in 3 per cent after treatment with "pyribenzamine." There were still other symptoms in a few cases.

A few other and special reports are interesting. Slater and Francis<sup>66</sup> describe the case of a truck driver who took a 50 mg. capsule of "benadryl" for his hay fever and two hours later went to sleep at the wheel. Children particularly show side reactions, varying from drowsiness to vomiting. Levin<sup>52</sup> observed them in 63 per cent of his 223 patients treated with "benadryl." McGavock and his associates<sup>47</sup> observed them in over half their cases. Using "pyribenzamine," Arbesman and his co-workers<sup>51</sup> observed side effects in 144 of 495 patients, or 29 per cent. It is true that in only 22 of these were the side effects severe, and the authors declare that danger from the drugs is not great, that disturbing symptoms may occur, but they pass off. Nevertheless, Geiger, Rosenfield and Hartman<sup>67</sup> report the case of a young woman, aged 26, with generalized seborrheic dermatitis, who was given 300 mg. of "benadryl" in the course of three days and then suddenly was found unconscious, cold, pale and pulseless. After the administration of epinephrine she revived.

Leukopenia and granulocytopenia has been observed to follow administration of the antihistaminic drugs, as they have followed administration of other drugs of complicated chemical structure. Cole of Cleveland<sup>68</sup> wrote me in November 1946: "I have known granulocytopenia to occur in several cases following the use of 'benadryl'." Blanton and Owens<sup>69</sup> describe a woman of 73 who had urticaria for seven weeks and was given "pyribenzamine," 200 mg. each day. She improved, and treatment with the drug was continued, 160 mg. each day. Twenty-five days later the symptoms recurred; her temperature rose to 103 F., and her white blood cell count fell to 1,300, with only 3 per cent polymorphonuclear leukocytes in the smear. Feinberg<sup>34</sup> ends his report with the note that "the remote toxicity from these drugs has not been sufficiently ascertained up to this time."

My results agree with those in the reports in the literature. In the summer of 1947, 82 patients with hay fever due to ragweed, who still

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66. Slater, B. J., and Francis, N.: Benadryl: A Contributing Cause of an Accident, *J. A. M. A.* **132**:212 (Sept. 28) 1946.

67. Geiger, J.; Rosenfield, S. Z., and Hartman, D. L.: Unusual Reaction Following Benadryl Administration, *J. A. M. A.* **133**:392 (Feb. 8) 1947.

68. Cole, H. N.: Personal communication to the author.

69. Blanton, W. B., and Owens, M. E. B., Jr.: Granulocytopenia Due Probably to "Pyribenzamine," *J. A. M. A.* **134**:454 (May 31) 1947.

had symptoms in spite of specific treatment, were given "benadryl" in average doses of 200 mg. a day. Of this group, 55, or 67 per cent, felt that the drug was helpful. Side effects were common, especially drowsiness, and some patients said that the hay fever itself was less troublesome than these side effects. The doses taken are variable, and this fact makes all reports of the specific effect irregular and difficult to compare. The practical point which develops from this is that the clinical use of any of these drugs requires careful attention to dosage. Whereas the 50 mg. capsule or tablet may cause drowsiness, if at the same time it relieves the sneeze or the itch, one may observe that half the quantity, or 25 mg., given only once or twice a day, especially at bedtime, will also provide relief, yet without producing symptoms which are disagreeable. The drowsiness will do good rather than harm. The sedative effect can be utilized as an advantage in place of a disadvantage. In children, and in adults too, even smaller quantities can be given if the drug is prescribed as a liquid mixture, of which a teaspoonful contains only 10 mg.

Other drugs in this series, in addition to "antergan" and "neoantergan," will be developed and marketed soon. They will be useful as adjuncts to the older methods of treatment, but they will not replace them.

*Comment.*—Since the principles which led to the development of these drugs are sound, it is proper to consider various reasons for the disappointing clinical effect. There are two main questions: First, are the drugs truly antihistaminic? Do they neutralize histamine in animals? Do they inhibit the known effects of histamine in human beings? Second, is histamine the cause of symptoms in each case, or can one say that different types of asthma, for example, have different mechanisms?

#### ARE THE NEW DRUGS TRULY ANTIHISTAMINIC?

As to the first question, the shock which follows the intravenous injection of histamine into guinea pigs can be prevented by previous treatment of the animals with antihistaminic drugs. Friedlaender, Feinberg and Feinberg<sup>70</sup> observed that animals treated with "benadryl" in doses of 3 mg. per kilogram of body weight could tolerate five lethal doses of injected histamine and that other animals treated with "pyribenzamine," 3 mg., could tolerate thirty-seven lethal doses. In the same experiment "antergan" was observed to protect against six lethal doses, while "neoantergan" injected in the same quantity could protect against one hundred and twenty-five lethal doses.

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70. Friedlaender, S.; Feinberg, S. M., and Feinberg, A. R.: Histamine Antamine Antagonists: V. Comparative Study of Benadryl and Pyribenzamine in Histamine and Anaphylactic Shock, *Proc. Soc. Exper. Biol. & Med.* 6:65, 1946.

Asthma may be experimentally induced in guinea pigs by exposing them to a spray of histamine aerosol. Loew and his associates<sup>71</sup> studied the protective effect of a number of compounds injected intraperitoneally fifteen minutes before the time of exposure to the spray and observed that all of the drugs protected in some degree. If the effect of aminophylline was 1, "benadryl" had an activity of 33. For comparison, although the mechanism of its action is different, epinephrine had an activity of 500. Mayer<sup>72</sup> observed that, whereas the histamine aerosol killed normal guinea pigs in about two and a half minutes, pretreatment of the animals with a single dose of "pyribenzamine," 0.10 mg. per kilogram of body weight, injected subcutaneously was enough to protect the animals unless the drug was given more than four hours before the test.

Experiments on the isolated muscle suspended in the Dale bath are even more direct. Loew and his co-workers<sup>73</sup> observed that "benadryl" was active in preventing the contraction when it was added to the bath in high dilution (1 to 25,000,000) just before the minimum effective dose of histamine (also in high dilution, 1 to 125,000,000). Mayer<sup>72</sup> observed that "pyribenzamine" was also effective: the addition of as little as 0.02 gamma per cubic centimeter (1 to 5,000,000) to the Dale bath neutralized as much as 1.0 gamma per cubic centimeter of histamine (1 to 1,000,000).

Loew and his co-workers<sup>73</sup> brought out the important point that "benadryl" can inhibit the contraction of the muscle strip when it is stimulated not only by histamine but also by such diverse substances as barium chloride and acetylcholine. The doses, however, are important. Against histamine, "benadryl" is effective in a dilution of 1 to 25,000,000 or 50,000,000, whereas against barium chloride a dilution of 1 to 10,000 was required. Against acetylcholine, "benadryl" is effective in a dose of 1 to 8,000,000, in contrast to atropine, which is effective in a concentration of 1 to 100,000,000. As the authors point out, the atropine-like qualities are increased at the expense of the antihistaminic effect. This atropine-like effect suggests that "benadryl" has an effect on the smooth muscle cells, or perhaps on the neuroeffector mechanism, which is in addition to its effect on histamine. However, this other property of "benadryl" requires much larger amounts for its effect, and Loew concludes that "benadryl" is essentially a specific inhibitor of histamine.

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71. Loew, E. R.; Kaiser, M. E., and Moore, V.: Effect of Various Drugs on Experimental Asthma Produced in Guinea Pigs by Exposure to Atomized Histamine, *J. Pharmacol. & Exper. Therap.* **86**:1, 1946.

72. Mayer, R. L.: Antihistaminic Substances with Special Reference to Pyribenzamine, *J. Allergy* **17**:153, 1946.

73. Loew, E. R.; MacMillan, R., and Kaiser, M. E.: The Antihistaminic Properties of Benadryl 6-Dimethylaminoethyl Benzhydryl Ether Hydrochloride, *J. Pharmacol. & Exper. Therap.* **86**:229, 1946.

Direct comparisons between the effect of the drug against histamine and the effect against the antigen-antibody reactions of anaphylaxis have been made. Yonkman and his associates<sup>74</sup> removed the lungs from guinea pigs sensitized to horse serum and perfused the organs by injecting isotonic solution of sodium chloride through the trachea, collecting the perfusate as it escaped from scratches made in the pulmonary surface. When the specific antigen-horse serum was added to the perfusion fluid, the escape of perfusate dropped off sharply. Bronchospasm was apparent. When, however, "pyribenzamine" was added to the perfusion fluid ten or twenty minutes before the horse serum, no change in the rate of perfusion occurred. The bronchospasm did not occur. When the lungs were perfused with histamine, it was observed that "pyribenzamine," added just before the test, could inhibit the normal resistance to the passage of fluid; this time the bronchospasm was prevented. The protection supplied by "pyribenzamine" against histamine, but not against the specific foreign serum reactions, is difficult to explain, especially as in anaphylactic shock in the whole animal "pyribenzamine" affords such good protection.

Rose and his co-workers,<sup>75</sup> using a different technic, did not come to all of the same conclusions. They observed that each of the antihistaminic drugs protected against anaphylactic shock in the guinea pig, and the fact that this protection diminished as the dose was decreased was considered as evidence that the shock was dependent on the release of histamine. On sensitized muscle strips, the drugs were effective against the anaphylactic contractions, and, more than that, the dose which was effective in that experiment was not enough to protect against a contraction of the same magnitude due to histamine. In explanations of the discrepancy that the drug can inhibit the reaction of the muscle strip sensitive to antigen better than it can inhibit the reaction of the normal strip to histamine, the authors point out that in active sensitization the histamine is in closer contact with the muscle cells, and this may be so. I, however, am skeptical of the premises, because the authors did not study the minimum quantity of histamine which could have produced a contraction "of that magnitude."

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74. Yonkman, F. F.; Oppenheimer, E.; Rennick, B., and Pellett, E.: Pharmacodynamic Studies of a New Antihistaminic Agent, Pyribenzamine (N, N-Dimethyl-N-Benzyl-N-[ $\alpha$ -Pyridyl]-Ethylene Diamine Hydrochloride): II. Effects on Smooth Muscle of the Guinea Pig and Dog Lung, *J. Pharmacol. & Exper. Therap.* **89**:31, 1947.

75. Rose, J. M.; Feinberg, A. R.; Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: VII. Comparative Antianaphylactic Activity of Some New Antihistaminic Drugs, *J. Allergy* **18**:149, 1947.

Halpern<sup>76</sup> has studied several new antihistaminic drugs. Each of these was effective in protecting the isolated muscle strip against histamine, and each prevented the development of asthma in guinea pigs after the administration of histamine aerosol. Substance "3015 R.P." (N-dimethylaminoethyl-thiodiphenylamine) protected a guinea pig against four hundred lethal doses of injected histamine, whereas "an-tergan" protected against only sixty doses. Against anaphylactic shock, however, 5.0 mg. per kilogram of body weight of "3015 R.P." was required, whereas only 1.0 mg. per kilogram of body weight of "antergan" was sufficient. Another substance, "3277 R.P." (N-dimethylamino-2-propyl-1-thiodiphenylamine), protected against anaphylaxis in a dose as small as 0.50 mg. per kilogram of body weight, and the standard quantity could protect the guinea pig against fifteen hundred lethal doses of injected histamine. This second substance, therefore, is ten times as active against histamine. As Halpern concludes: "One is obliged to recognize that the antianaphylactic shock action of this series of substances does not run parallel with their antihistaminic activity."

Cutaneous tests, intradermal injections of various substances, were done on rabbits by Last and Loew.<sup>77</sup> Pretreatment of the animals with "benadryl" or "neoantergan" blocked the reactions to the test with histamine, but had no effect on the reactions to intradermal injections of trypsin, snake venom or codeine in normal animals, and, more important, there was no effect on the reaction to horse serum in sensitized rabbits. This last is in contrast to the effect in allergy in human beings, in whom, as will be shown, pretreatment tends to inhibit the specific cutaneous reaction.

The effect on the stomach of dogs and the effect on mice is interesting. It suggests a synergistic action of "benadryl.". When "benadryl" in wax and histamine in wax were given simultaneously and daily to 7 dogs, gastric and/or duodenal ulcerations developed in all, according to Friesen, Baronofsky and Wagensteen.<sup>78</sup> Mice were treated by Mayer and Brousseau<sup>79</sup> with a mixture of "pyribenzamine or "benadryl" and histamine, and the animals died from doses which were smaller than the doses used when each drug had been given separately.

76. Halpern, B. N.: Experimental Research on a New Series of Chemical Substances with Powerful Antihistaminic Activity: The Thiodiphenylamine Derivatives, *J. Allergy* **18**:263, 1947.

77. Last, M. R., and Loew, E. R.: Effect of Antihistamine Drugs on Increased Capillary Permeability Following Intradermal Injections of Histamine, Horse Serum and Other Agents in Rabbits, *J. Pharmacol. & Exper. Therap.* **89**:81, 1947.

78. Friesen, S. R.; Baronofsky, I. D., and Wagensteen, O. H.: Benadryl Fails to Protect Against Histamine-Provoked Ulcer, *Proc. Soc. Exper. Biol. & Med.* **63**:23, 1946.

79. Mayer, R. L., and Brousseau, D.: Antihistaminic Substances in Histamine Poisoning and Anaphylaxis of Mice, *Proc. Soc. Exper. Biol. & Med.* **63**:197, 1946.



In human beings simple experiments show the antihistaminic effect of these drugs. That histamine will produce a typical wheal-erythema reaction to a cutaneous test is well known. Friedlaender and Feinberg<sup>54</sup> gave 50 mg. of "benadryl" by mouth three times a day for a week, and then made cutaneous tests with histamine in normal persons as well as with the specific antigen in allergic patients. With this dose, there was no change in the subsequent cutaneous reactions, but, when the dose was increased to 100 mg. and given one hour before the test, the reactions were milder after than before the treatment with the drug, but the eruptions did not disappear. When the drug was mixed in the test tube with the histamine or the antigen beforehand, the cutaneous reactions were reduced in all instances.

Cohen and his co-workers<sup>80</sup> gave their patients "benadryl," 50 mg. four times a day, and then made cutaneous tests with dilutions of histamine, by the method of iontophoresis. Their subjects were protected against an average of eight times the whealing dose. They also made cutaneous tests with mixtures of histamine and "benadryl," but, unlike the previous investigators, they could not demonstrate that "benadryl" prevented the usual histamine response. Arbesman and his co-workers<sup>81</sup> have also studied wheals due to histamine and observed that "pyribenzamine" given by mouth in doses of 50 to 150 mg., and taken forty-five minutes before the cutaneous tests were repeated intradermally with histamine dilutions, caused a decrease in both histamine and allergic wheals in about two thirds of the cases. More recently McGavack and his co-workers<sup>47</sup> repeated Friedlaender's experiments on whealing, and their results were irregular.

The specific effect of histamine on the gastric secretions offers another means of studying the antihistaminic effect. Loew and his co-workers<sup>73</sup> observed that "benadryl" inhibits from 40 to 80 per cent of the normal response in human beings.

In summary, in answer to the first question "benadryl" and "pyribenzamine" can neutralize histamine both in animals and in human beings, and this effect is specific. In human beings, on the other hand, as in anaphylaxis and in experiments involving antigen-antibody reactions, the effects of the drugs are rather irregular.

• IS HISTAMINE THE CAUSE OF SYMPTOMS IN EACH CASE?

In answer to the second question, whether the irregular results in the use of these drugs can throw any light on the mechanisms of allergic

80. Cohen, M. B.; Friedman, H. J.; Zomis, J.; Burke, M., and Abram, L. E.: The Effect of Beta-Dimethylaminoethyl-Benzhydryl-Ether-Hydrochloride on the Histamine Threshold of Human Skin, *J. Allergy* 18:32, 1947.

81. Arbesman, C. E.; Koepf, G. F., and Miller, G. E.: Some Antianaphylactic and Antihistaminic Properties of N'Pyridyl, N'Benzyl Dimethylenediamine Monohydrochloride (Pyribenzamine), *J. Allergy* 17:203, 1946.

diseases, the drugs are not so effective in asthma as they are in hay fever and urticaria. It is possible that this difference indicates a different mechanism in different cases, but so far there are no data to support such a thesis. Wagner<sup>49</sup> observed that "benadryl" was twice as effective in asthma which was seasonal as it was in asthma which was intrinsic, but Waldbott<sup>48</sup> saw no such distinction. It is fair to point out that even in hay fever, which appears to be a uniform disease with a simple and well defined cause, the results vary between 52 and 94 per cent, and the best average is not more than 77 per cent. If now the results in hay fever are so far from uniform, what use is there to speculate on the irregularities in asthma? The one fact that the drugs are not 100 per cent effective is important. It suggests that histamine is not the only mechanism for symptoms. There is probably a fallacy in this argument which depends on the difficulty of appraising the clinical results. Is it likely that each author used the same dosage and continued the use of the drug for the same number of days in each patient? Was he careful to include in his report only those patients who had received minimum treatment, and what was this minimum? Did the untoward reactions make many patients give up treatment with the new drug? Is it not probable that a more critical study would yield a better correlation of the results?

Meantime, Loew<sup>35</sup> reports other actions of antihistaminic drugs: in anesthetized animals they stimulate respiration, with depression later. Blood pressure may fall at first and rise later; the changes are not too perceptible. The drugs prevent histamine from relaxing the smooth muscle of systemic arterioles and coronary vessels. They have some local anesthetic action. Large doses in animals will cause hyperexcitability, with tremor and convulsions. The effectiveness of the drugs in anaphylaxis and allergy depends on their ability to block the effects of histamine on smooth muscle, both vascular and visceral.

The second question, therefore—whether histamine is the cause of symptoms in each case—can be answered only by saying that the evidence at hand suggests that, since the antihistaminic drugs are so much more active against histamine than they are against allergic reactions, the latter are due to factors other than, or in addition to, histamine. Sir Thomas Lewis was wise to designate the intermediary factor as "H substance," and for the present it is best to retain that broad and all-inclusive designation.

Whether further study of the free histamine in the blood plasma will show that it varies directly with the severity of symptoms is perhaps doubtful, but the question should be answered. On the whole, the case for histamine itself, as the mediating factor in allergic disease, is not good enough. Must consideration be limited to the filtrate which remains when the blood sample is boiled with acid? The clinician is

obliged to think of an active substance or principle which arises in the body, often rather suddenly, from a variety of exciting factors: from allergic reactions in young patients, but from infections of various kinds, and from the vague disturbances of somatic and of psychic depletion, or stress and strain, in the older patients. There is no doubt about the acute suffering which ensues. The symptoms suggest "poisoning" of some sort. They are relieved by treatment with epinephrine, aminophylline and, especially, fluid given in quantity intravenously, but the antihistamine drugs are not good enough for them. What are the other possible mediators?

Selye<sup>82</sup> describes the adaptation syndrome as an explanation of the characteristic group of symptoms (systemic reactions) which develop from stress, and the stress includes the effect of noxious agents in considerable variety. Physical injuries—wounds, fractures and burns—excite the "alarm reaction," which is the first part of the syndrome, but injuries which are less violent, like cold or anorexia from high altitude, can do it, as well as poisonings from drugs and chemicals. Most important to me, the concept includes the idea that fatigue and the stress and strain from emotional factors can produce the same syndrome. I believe that Selye's theory is plausible. The pathologic changes which he has described, and which will be noted later, are comparable to the changes seen in allergic disease. So far Selye has not considered the release of histamine or other hormone as the mediating substance in his syndrome. Rose, however, has studied the matter. In experiments not yet published, he was unable to demonstrate any significant change in the histamine in the blood in rats during various stages of the "alarm reaction." Selye's theory is that the reactions depend on changes in the secretion of the adrenal cortex, or rather in the corticotropic hormones from the pituitary which stimulate the adrenal cortex to produce its hormones with their three general functions: the 17 ketosteroids, including the testoid hormone, the salt-active corticoids, like desoxycorticosterone (a synthetic compound of the adrenal cortex), and the sugar-active corticoids. (Selye is discussed again in part II, under "Pathologic Changes.")

Forbes points out that Forsham and his co-workers,<sup>82a</sup> Bartter and his co-workers<sup>82b</sup> and others have produced "alarm reactions" in human

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82. Selye, H.: The Alarm Reaction, in Piersol, G. M., and Bortz, E. L.: *Cyclopedia of Medicine, Surgery and Specialties*, ed. 2, Philadelphia, F. A. Davis Company, 1940; *Diseases of Adaptation*, *J. Allergy* **17**:231, 289 and 358, 1946; *General Adaptation Syndrome and Diseases of Adaptation*, *J. Clin. Endocrinol.* **6**:117 1946.

82a. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: *Clinical Studies with Pituitary Adrenocorticotropin*, *J. Clin. Endocrinol.* **8**:15, 1948.

82b. Bartter, P.; Albright, F., and Forbes, A. P., in *Conference on Metabolic Aspects of Convalescence*, New York, Josiah Macy Jr. Foundation, 1945.

subjects by injecting pituitary adrenocorticotrophic hormone. There was diuresis of potassium, calcium and phosphorus, with retention of sodium. There was loss of nitrogen and uric acid and increase of the polymorphonuclear white cells, with decrease in the lymphocytes and disappearance of the eosinophils. There was elevation of the blood pressure in 1 case. Whether further study will show that these features will occur in asthma remains to be seen. Since the 17-ketosteroid excretion has been observed to be lower than normal in patients with asthma, Forbes suggests the possibility that in these patients, because of exhaustion of the adrenal gland by repeated alarms, the usual healthy reaction to stress may be altered.

In the meantime, patients are conditioned for the development of "allergic disease." Other patients suffer the same sort of infections and the same sort of stress and strain, but arthritis develops in place of asthma, presumably because they are conditioned that way, because they were born with a "Y" instead of an "X" factor. This is another vital problem. Is there an approach to it?

## PART II. PATHOLOGIC ASPECTS, DIAGNOSIS AND TREATMENT

Several good books on allergy appeared in 1946 and 1947. The second edition of a large volume entitled "Allergy," by Urbach and Gottlieb,<sup>83</sup> is indeed a complete work. It has nine hundred and sixty-eight large pages, with two columns to the page. It covers every phase of the subject; it refers to almost every paper which bears on allergic disease that has been written in recent years.

The second edition of Feinberg's "Allergy in Practice"<sup>84</sup> also appeared in 1946. This book is complete, if not so all-inclusive. It has eight hundred and thirty-eight pages, but they are of average size and more readable than those of the first edition. More important, the author is critical and selects his references with care. His discussion is complete and sound. Many chapters have over a hundred references listed at the end. Important topics are given the relatively more attention which they require.

"The Diagnosis and Treatment of Bronchial Asthma" by L. H. Gay<sup>85</sup> is a smaller book. Its three hundred and thirty-four pages deal with asthma only, and the discussion is built up around a great number of reports of cases. It is a clinical study and makes interesting reading. The author does not attempt to elaborate on the physiologic and immunologic aspects of the disease, but the pathologic aspects of asthma are

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83. Urbach, E., and Gottlieb, P. M.: *Allergy*, ed. 2, New York, Grune & Stratton, Inc., 1946.

84. Feinberg, S. M.; Durham, O. C., and Dragstedt, C. A.: *Allergy in Practice*, ed. 2, Chicago, The Year Book Publishers, Inc., 1946.

85. Gay, L. N.: *The Diagnosis and Treatment of Bronchial Asthma*, Baltimore, Williams & Wilkins Company, 1946.

described well. The book reflects the author's wide experience in the clinic at Johns Hopkins Hospital.

The "Treatment of Bronchial Asthma," by Derbes and Engelhardt,<sup>86</sup> is a moderate volume of four hundred and sixty-six pages. It is not a monograph, like the books mentioned; it is a compendium, with the different chapters written by different authors. The editors, however, have written eight of the twenty-three chapters. The emphasis is on cutaneous tests, and on the description of allergenic substances, pollens, dusts and foods. There is an interesting chapter, "Anatomy and Physiology of the Respiratory Tract," by G. E. Burch of Tulane University, but the chapter on immunology, by M. B. Cohen, is too much simplified.

Cooke's "Allergy in Theory and Practice"<sup>87</sup> is also a compendium, but Cooke himself has written twelve of the thirty-two chapters, as well as the appendix. There are five hundred and seventy-two pages. The principles and theories of allergy are discussed in able fashion, and opposing views are described. There are one or two unnecessary pictures, but there is none of the padding by photographs of plants, pollens and cutaneous lesions which have appeared elsewhere. Every student of allergy needs this book.

#### PATHOLOGIC ASPECTS OF ALLERGIC DISEASE (RICH AND SELYE)

The pathologic aspects of allergic disease are becoming more understood, chiefly because of studies under way in the laboratories of Rich<sup>88</sup> of Johns Hopkins University and Selye<sup>82</sup> of Montreal, Canada. That this is a new development is shown by the short treatment in the textbooks just described. The enormous work of Urbach and Gottlieb devotes only three pages to the pathologicoanatomic aspects of allergy with the histologic aspects of allergic reactions. In another section, however, vascular lesions, including periarteritis nodosa, receive better treatment. Feinberg treats symptoms and pathologic changes together with periarteritis, which appears at the end of the book under miscellaneous topics. Gay, dealing with asthma, describes the pathologic aspects of asthma, giving many reports of cases and tables. Periarteritis is described. Derbes and Engelhardt describe the clinical pathologic aspects.

In Cooke's book is Klemperer's<sup>89</sup> discussion of the pathologicoanatomic aspects of allergy. First of all, there is no one lesion which is produced in the antigen-antibody reaction and in no other injury. The outpouring

86. Derbes, V. J., and Engelhardt, H. T.: *The Treatment of Bronchial Asthma*, Philadelphia, J. B. Lippincott Company, 1946.

87. Cooke, R. A.: *Allergy in Theory and Practice*, Philadelphia, W. B. Saunders Company, 1947.

88. Rich, A. R.: *The Significance of Hypersensitivity in Infections*, *Physiol. Rev.* **21**:70, 1941.

89. Klemperer, P.: *Pathologic-Anatomic Aspects of Allergy*, in Cooke,<sup>87</sup> p. 69.

of eosinophils is characteristic, but it is not specific. The problem is complex because of the two phases of the reaction. When foreign protein meets its specific antibody on the surface of the tissue cell, the typical response is an immediate wheal and erythema reaction. In mild reactions there is local edema with moderate infiltration of cells, many of which are eosinophils, but in severer reactions the process involves the endothelium of blood vessels and involves the collagen to produce fibrinoid degeneration of the connective tissue. The so-called Arthus phenomenon, with necrosis resulting primarily from the damage to the blood vessels, represents the end stage. It is produced most easily in the skin of the sensitized rabbit, but it may occur in other tissues and in other animals also. As Zinsser<sup>90</sup> showed originally, this immediate reaction requires a high concentration of antibodies, and thus this special kind of inflammatory reaction represents the late stage of the allergic process. The tuberculin reaction is different. It is "allergic" because it also requires the participation of factors in the tissue of the host. However, it requires less antibodies and so may often be elicited in the early phase of the process, before the animal is "ready" for the reactions of the immediate type. This reaction appears twenty-four hours after the last dose; it is delayed. Whereas Dienes and Mallory<sup>91</sup> described certain histologic differences between the immediate and the delayed types of response, Klemperer states that in strong reactions the difference is not evident. Meantime, the whole problem of bacterial allergy is complicated by the primary toxicity of bacteria and their products, which cause changes without the aid of the host-tissue factor.

The studies made by Rich<sup>88</sup> and by Selye<sup>82</sup> have advanced knowledge greatly. The concept of the pathogenesis of the allergic diseases has been broadened: First, the background of such allergic manifestations as asthma and eczema has been improved by the better understanding of the basic reactions involved. Second, similar reaction patterns have been seen in other diseases, so that allergy is recognized as a factor in the pathogenesis of such diseases as rheumatic fever and perhaps glomerulonephritis. Other conditions in which the histologic observations include fibrinoid degeneration of the colloid may turn out to depend on a mechanism which includes allergic reactions. Thromboangitis obliterans, lupus erythematosus, scleroderma and perhaps interstitial nephritis may be studied from this new viewpoint. The variety of acute endocarditis which is nonbacterial and is called Libman-Sacks disease, from its original describers,<sup>92</sup> is in the same group. To include these

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90. Zinsser, H.: Studies on the Tuberculin Reaction and on Specific Hypersensitiveness in Bacterial Infection, *J. Exper. Med.* **34**:495, 1921.

91. Dienes, L., and Mallory, T. P.: Histological Studies of Hypersensitive Reaction, *Am. J. Path.* **8**:689, 1932.

92. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33**:701 (June) 1924.

obscure conditions in the allergic concept at this time is somewhat bold, but at least the idea is interesting. How did it come about?

*Periarteritis Nodosa (Loeffler's Syndrome).*—In 1942 Rich<sup>93</sup> observed 7 patients who died and who had presented a clinical syndrome like that of serum disease. They had fever and prostration, but the typical symptom was a diffuse urticarial rash which suggested poisoning of some sort. At autopsy in 4 of the cases, the typical lesions of periarteritis nodosa were shown—the familiar picture of necrosis with fibrinoid degeneration, hyalinization, hemorrhage and eosinophilia. Rich pointed out that this type of disease was new; it had appeared during the year when sulfonamide drugs were first used in large doses and in many patients, and the first question was whether the illness and the characteristic pathologic changes depended on the primary infection which had made the patient ill in the first place or whether it was the serum used in treatment or the sulfonamide drug, or a combination of these three factors.

In the meantime, other workers, starting with Kussmaul and Maier<sup>94</sup> in 1866, have described periarteritis nodosa in character, if not in name, and the condition did occur occasionally in patients treated with large doses of foreign serum. In 1943 Rich and Gregory<sup>95</sup> selected 14 large rabbits; into 9 of them was injected horse serum in doses of 10 cc. per kilogram of body weight, an enormous quantity. Five of the rabbits received, in addition, sulfadiazine in doses of 0.5 Gm. per kilograms of body weight. On the twelfth day cutaneous tests showed that all the rabbits were hypersensitive to horse serum, and on the seventeenth day all were inoculated with 1 cc. of horse serum. Two of the animals died, and later the others were killed. At autopsy every stage of periarteritis nodosa could be seen in these rabbits. It was obvious that the blood vessels had become the seat of severe anaphylactic injury. Later, it was observed that one large dose of serum was enough to cause the lesions and that the addition of sulfadiazine was not essential in producing the injury to the blood vessels. As expected, the kidneys of these animals showed severe focal lesions of the glomeruli; the process of allergy is evidently concerned with the pathologic changes of glomerulonephritis.

The lesion is comparable to the lesion of the Arthus phenomenon and is different from the lesion observed in reactions to bacteria of the tuberculin type. Before the Academy of Allergy, in December 1945,

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93. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull. Johns Hopkins Hosp.* **71**:123, 1942.

94. Kussmaul, A., and Maier, R.: Periarteritis Nodosa, *Deutsches Arch. f. klin. Med.* **1**:484, 1866.

95. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *Bull. Johns Hopkins Hosp.* **72**:65, 1943.

Scherp<sup>96</sup> reviewed the differences between the Arthus reaction and the tuberculin reaction. The Arthus reaction depends on vascular damage, as Rich demonstrated. The tuberculin reaction, however, depends on the destruction of sensitized cells near, but outside, the blood vessels. Circulating antibody is important for the Arthus reaction, and its severity depends on the concentration of these antibodies. The tuberculin reaction, however, is also a specific phenomenon; the animal reacts only when treated with the organism which primarily sensitized it, and antibodies are necessary, but the point is that these antibodies are attached to the cells and are not free in the circulating blood. The subject is discussed well by Rich<sup>88</sup> in his paper in *Physiological Reviews* (1941). In that paper the significance of hypersensitivity in infections is discussed. More recently Rich has pointed to the fact that, whereas before sulfonamide drugs came into general use only 6 cases of periarteritis nodosa had been seen at the Johns Hopkins Hospital, since then 32 cases have been discovered. Also, the localized lesions, called "Aschoff bodies," seen in rheumatic carditis have a periarterial location, which makes them comparable to the lesions in periarteritis nodosa, and that, in turn, identifies them as another manifestation of allergy. A useful review of this subject is in a recent paper by Bohrod.<sup>97</sup>

Selye<sup>82</sup> also has produced the lesions of periarteritis nodosa, but by a different principle. "Desoxycorticosterone," the salt-active corticoid of the adrenal cortex, when given in large doses to normal animals, will give rise to vascular lesions identical with those seen in periarteritis nodosa, to myocardial and joint lesions similar to those in rheumatic fever, to nephrosclerosis and sometimes to acute nephritis. This occurs more intensively when large amounts of sodium chloride are given by mouth at the same time. There is a retention of sodium and a loss of potassium, but the latter is not important, for the addition of potassium chloride does not prevent the lesions. On the other hand, the ammonium salts, chloride and sulfate, will protect the animal against the effect of "desoxycorticosterone," perhaps because the elimination of sodium is enhanced. The pictures in Selye's paper show well that lesions of many organs occurred in the animals treated either with anterior pituitary material containing the corticotropic hormone or with "desoxycorticosterone acetate," and salt. Foci and arterial lesions in the myocardium, ulcerations in the stomach, thrombi in the mesentery, arterial lesions in the brain, glomerular lesions in the kidney and inflammation of the joints are all depicted.

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96. Scherp, H. W.: Hypersensitivity to Infectious Agents in Relation to Asthma, *J. Allergy* 17:255, 1946.

97. Bohrod, M. G.: Classification of the Histologic Reactions in Allergic Diseases, *Am. J. Med.* 3:511, 1947.



Comparison of the works of Rich and Selye is interesting. Rich produced periarteritis with sulfonamide drugs in the presence of infection and also with foreign serum in large doses. Selye produced the same type of lesions with a glandular extract and more pronounced lesions with the addition of salt. Several questions arise: Is an antigen-antibody reaction essential? Does Selye's "desoxycorticosterone" produce antibodies to itself? Selye and Pentz<sup>98</sup> have demonstrated that periarteritis can be produced by a variety of nonspecific damaging agents, including exposure to cold. This last is important because it encourages the idea that in patients with asthma it is not necessary to consider an antigen-antibody reaction, an allergy in each case; the concept of depletion resulting from stress and strain is evidently satisfactory, provided only that asthma be considered as one of the "diseases of adaptation."

If this is true, why is periarteritis nodosa such a rare development in asthma? In 1939, Rackemann and Greene<sup>99</sup> described 8 patients in whom this pathologic change developed as a complication of asthma of maximum severity. Usually the lesions are not seen. Since some of the patients have recovered, it is evident that the lesions may heal of themselves, and it may be possible that under ordinary conditions they are not recognized.

An observation by Hawn and Janeway<sup>100</sup> is important. In studying the reactions of normal rabbits to the purified fractions of serum, they observed that it was the albumin fraction which was particularly prone to produce lesions of the arteries. Injections of beef gamma globulin caused injuries of the liver and kidneys, while involvement of the arteries generally was less conspicuous. Also, they observed that the acute lesions developed only during the time that the antigen was present in the circulating blood. As soon as the antibodies began to appear, healing of the lesions proceeded rapidly. The observations support the idea that periarteritis nodosa is a temporary process which can come and go. It may be commoner than is recognized, for recovery can occur as immunity develops and as the general condition of the patient improves.

New cases of periarteritis nodosa are reported. Contratto<sup>101</sup> describes a man of 40 who had pulmonary tuberculosis when he was a student. At age 34, attacks of fever and malaise developed. Small nodes were seen under the skin of his forearm; one of these was excised,

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98. Selye, H., and Pentz, E. I.: Pathogenetic Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, *Canad. M. A. J.* **49**:264, 1943.

99. Rackemann, F. M., and Greene, J. E.: Periarteritis Nodosa and Asthma, *Tr. A. Am. Physicians* **54**:112, 1939.

100. Hawn, C. V., and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, *J. Exper. Med.* **85**:571, 1947.

101. Contratto, A. W.: Periarteritis Nodosa: A Report of Two Cases, One with Special Reference to Sensitivity Factors, *Arch. Int. Med.* **80**:567 (Nov.) 1947.

and the lesions of periarteritis nodosa were demonstrated. He rested for a year and then went back to work, but other attacks occurred. He never was really ill. Another of the nodes, excised later, showed lesions of active tuberculosis. Ultimately the man recovered. In this case the arterial lesions were closely related to the tuberculosis. Higgins<sup>102</sup> reports 6 cases, demonstrating the multiplicity of pathologic and clinical manifestations characteristic of this generalized disease. Lichtenstein and Fox<sup>103</sup> saw typical lesions in a woman who died three weeks after an operation on her shoulder. At the time of the operation 5 Gm. of sulfathiazole had been shaken into her wound, and nine days later she experienced a sudden chill with fever and a generalized cutaneous eruption. More sulfathiazole, a quantity of 31.5 Gm., was given during the following six days, until she died. Obviously there was intoxication from too much medication in a patient who had become sensitized.

Werne and Garrow<sup>104</sup> report the cases of identical twins, both of whom had severe reactions following the administration of second doses of diphtheria toxoid and pertussis antigen. It is important that the first injection, given a month previously, had made the children sick with vomiting and fever, and after the second injection both were seriously ill and 1 of them died. At autopsy, lesions "consistent with anaphylactic shock" were demonstrable, but more important, a series of vascular lesions seen in all the organs made a characteristic picture of periarteritis nodosa. I noted that in each of these "new cases" an antigen-antibody mechanism could be considered as operative. Other cases without this mechanism should be found.

Loeffler's syndrome, transitory infiltrations of the lungs, may come and go with surprising speed. Wright and Gold<sup>105</sup> observed the roentgen shadows to come and go in patients with creeping eruption due to cutaneous helminthiasis; 4 cases were reported by Blanton.<sup>106</sup> Henderson and Pierce<sup>107</sup> point out that the diagnosis of Loeffler's syndrome requires that roentgenograms of the chest be taken at frequent intervals. Herbut

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102. Higgins, W. H.: Periarteritis Nodosa: Clinical Manifestations and Post-mortem Findings with a Report of Six Cases, *South. M. J.* **39**:453, 1946.

103. Lichtenstein, L., and Fox, L. J.: Necrotizing Arterial Lesions Resembling Those of Periarteritis Nodosa and Focal Visceral Necrosis Following Administration of Sulfathiazole: Report of a Case, *Am. J. Path.* **22**:665, 1946.

104. Werne, J., and Garrow, I.: Fatal Anaphylactic Shock: Occurrence in Identical Twins Following Second Injection of Diphtheria Toxoid and Pertussis Antigen, *J. A. M. A.* **131**:730 (June 29) 1946.

105. Wright, D. O., and Gold, E. M.: Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis): Report of Twenty-Six Cases, *Arch. Int. Med.* **78**:303 (Sept.) 1946.

106. Blanton, H. W.: Observations on Loeffler's Syndrome-Report of Four Cases, *Virginia M. Monthly* **72**:473, 1945.

107. Henderson, A. T., and Pierre, C. B.: Transitory Focal Pulmonary Edema and Eosinophilia: Loeffler's Syndrome, *Am. J. Roentgenol.* **58**:391, 1947.

and Kinsey<sup>108</sup> injected horse serum into the trachea of sensitized rabbits and produced dyspnea comparable with asthma. Roentgenograms of the lungs showed transitory pulmonary infiltration in these rabbits. So far the pathologic changes of Loeffler's syndrome are not clear, for the condition is mild and patients do not die from it. Usually the appearance in the roentgenogram is accompanied with a high percentage of eosinophils in the blood smear.

A recent paper by Gregory and Rich<sup>109</sup> throws light on Loeffler's syndrome. Rabbits were given repeated intravenous injections of foreign protein, and, when some of them died in acute anaphylactic shock, study of the lungs showed small focal lesions with damage of the capillary wall, thrombosis and edema. In other animals which survived the treatment and were killed later, similar lesions were seen; they were comparable to the type of local lesions seen in the lung in rheumatic fever. Longcope<sup>110</sup> inoculated animals in 1914; dogs, cats and guinea pigs were sensitized to egg white alone, to horse serum alone or sometimes to both at the same time. After reinjection, focal infiltrations of the heart and kidneys were plainly visible. The observations should have led to a much longer series of experiments, for they were basically the same as those which Rich describes.

In tropical eosinophilia (called Weingarten's syndrome), asthma appears to be a fairly common symptom. However, the asthma and the syndrome itself can be cured rather easily with a few injections of arsenic compound, like neoarsphenamine, or sometimes simply with carbarsone pills given by mouth. The 2 patients whom Irwin<sup>111</sup> describes were treated with carbarsone and recovered completely. Another case is reported by Hunter<sup>112</sup>—asthma developed in a young man who had spent twelve years in Nigeria in about six months after he had returned to England. His blood smear showed up to 74 per cent of eosinophils. Three injections of an organic arsenic preparation cured him.

Loeffler's syndrome and tropical eosinophilia are much alike. Arsenic compound cures the latter. Will it also cure Loeffler's syndrome? Is cure by arsenic compound a differential point? The question is not yet answered, presumably because the disease occurs rarely or, at least, it is not recognized, in this country.

108. Herbut, P. A., and Kinsey, F. R.: Transitory Pulmonary Infiltrations (Loeffler's Syndrome) in Rabbits, *Arch. Path.* **41**:489 (May) 1946.

109. Gregory, J. E., and Rich, A. R.: Experimental Production of Anaphylactic Pulmonary Lesions with the Basic Characteristics of Rheumatic Pneumonitis, *Bull. Johns Hopkins Hosp.* **78**:1, 1946.

110. Longcope, W. T.: Effect of Repeated Injections of Foreign Protein on the Heart Muscle, *Arch. Int. Med.* **15**:1079 (June) 1915.

111. Irwin, J. W.: Tropical Eosinophilia, *Ann. Int. Med.* **25**:329, 1946.

112. Hunter, E. A.: A Case of Tropical Eosinophilia (Weingarten's Syndrome), *Brit. M. J.* **1**:877, 1946.

## DIAGNOSIS OF ASTHMA

In an army general hospital, Rosen<sup>113</sup> studied 100 consecutive cases of asthma. He observed nasal symptoms in 45 and observed that they came before the asthma in about half the cases. Positive reactions to cutaneous tests occurred more frequently in the group of patients with nasal symptoms. Unger and his co-workers<sup>114</sup> classified the disease in their 97 cases into paroxysmal and chronic types. In all, 21.1 per cent of the patients were "cured," and, as expected, the better results were in the paroxysmal series. Waldbott<sup>115</sup> asks, "Is there an intrinsic asthma?" He selected 323 patients as having continuous symptoms. Positive reactions to cutaneous tests were seen in as many as 77 per cent, but the significance of these is not discussed. He recognizes that intrinsic causes—sensitivity to cold temperature, to endocrine products and to bacterial infections—"were definitely responsible for attacks in a large number. . . . Psychogenic factors, products of digestion or such physiological fluids as insulin, liver extract, colostrum may or may not play a part. In no case were such intrinsic factors found to be the only causes. . . ." Only 9 per cent of his patients were "cured." This type of disease is always difficult to deal with, since the cause is rarely simple or single, but it is my opinion that intrinsic factors, notably depletion, or stress and strain of various kinds, represent the important point. Waldbott has been frank enough to include an addendum to one report of a case: ". . . after being placed on a high caloric diet disregarding all positive foods, this patient has been practically free from asthma."

The chemical factors in asthma have been reviewed by Wiswell and Rackemann<sup>116</sup> in a study of the literature. It was observed that, so far at least, there is no evidence that disturbances of sodium, potassium or calcium or other metabolic factors play any constant role.

There are two interesting papers on bullous emphysema. Price and Teplick<sup>117</sup> describe 8 cases in which areas in one or other lobe, mostly in the apexes, is replaced by a cystlike area. Autopsy in 1 case showed two large sacs, with extremely thin walls, in which the air was under

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113. Rosen, F. L.: Bronchial Asthma in the Young Male Adult: A Study of One Hundred Hospitalized Patients in an Army General Hospital, with Special Reference to Nasal Symptoms and Findings, *Ann. Allergy* 4:247, 1946.

114. Unger, L.; Levy, H. A., and Eisele, I. B.: Outline on Bronchial Asthma, Scientific Exhibit, American Medical Association, Atlantic City, N. J., June 9-13, 1947.

115. Waldbott, G. L.: Is There an Intrinsic Asthma? *Ann. Int. Med.* 26:863, 1947.

116. Wiswell, J. G., and Rackemann, F. M.: Chemical Factors in Asthma, *New England J. Med.* 237:364 and 400, 1947.

117. Price, A. H., and Teplick, G.: Progressive Bilateral Bullous Emphysema, *Ar n. Int. Med.* 77:132 (Feb.) 1946.

pressure. All of their patients were men, and in all but 1 symptoms developed after the age of 45. Amberson and Spain<sup>118</sup> found the cause in their patient. A Negro, aged 44, had had wheezy colds, with persistent asthma later and then pneumonia. Autopsy showed that around many of the smaller bronchi there was a submucous organizing inflammation which encircled the airway to act as a check valve. During expiration, deflation of the bullae was much retarded. It is suggested that emphysema in later years may be referable to the proliferative changes with fibrosis around the bronchi which have followed early infectious processes.

#### TREATMENT OF ASTHMA

*Drugs.*—Epinephrine: Drugs are essential for the acute asthmatic attack. The recent literature says little about epinephrine, except that clinical reports here and there indicate that physicians have learned to use only small doses. For subcutaneous injection, a quantity as small as 0.25cc. of the 1 to 1,000 solution is often as effective, if not more so, than the large dose of 1 cc., which results in disagreeable side effects.

Aminophylline: Next to epinephrine in usefulness comes aminophylline for the relief of acute paroxysms. The usual dose is 0.25 Gm. dissolved in 10 cc. of isotonic sodium chloride solution and injected into the vein. Goodall and Unger<sup>119</sup> recommend the continuous injection of aminophylline, 2 or 3 Gm. in 2,000 cc. of 5 per cent dextrose solution in water. As much as 3.0 Gm. can be injected in this way in twenty-four hours without danger. Prigal, Fuchs and Schulman<sup>120</sup> report that suppositories containing 0.50 Gm. each were helpful to 25 out of 45 patients but that when 0.10 Gm. of pentobarbital sodium was added to the same amount of aminophylline in suppository form the mixture relieved 44 out of 47 patients. Evidently there is good reason for adding small doses of phenobarbital to the numerous pills and capsules now on the market, most of which contain ephedrine (25 mg.), aminophylline (250 mg.) and phenobarbital (10 mg.). Prigal, Brooks and Harris<sup>121</sup> describe the inhalation of aminophylline by means of an aerosol in steam. The steam passes into the nebulizer to carry with it small amounts of the solution of aminophylline contained therein.

118. Amberson, J. B., and Spain, D. M.: A Mechanism Explaining Chronic Progressive Pulmonary Bullous Emphysema, *Tr. A. Am. Physicians* 60:92, 1947.

119. Goodall, R. J., and Unger, L.: Continuous Intravenous Aminophyllin Therapy in Status Asthmaticus, *Ann. Allergy* 5:196, 1947.

120. Prigal, S. J.; Fuchs, A. M., and Schulman, P. M.: Treatment of Asthma with Rectal Suppositories of Aminophylline and Sodium Pentobarbital, *J. Allergy* 17:119, 1946.

121. Prigal, S. J.; Brooks, A. M., and Harris, R.: Treatment of Asthma by Inhalation of Aerosol of Aminophylline, *J. Allergy* 18:16, 1947.

Alcohol: Brown<sup>122</sup> suggests that alcohol can be injected safely as a 5 per cent solution in isotonic solution of sodium chloride, together with 5 per cent solution of dextrose. Five out of 6 of his patients with severe asthma were relieved with this treatment.

Procaine Hydrochloride: The administration of procaine hydrochloride intravenously is a new idea. In 1946 State and Wagensteen<sup>123</sup> observed that as much as 1.0 Gm. of procaine hydrochloride dissolved in 500 cc. of isotonic sodium chloride solution could be injected intravenously without harm. When given to 16 patients with serum sickness, it effected immediate and complete relief from itching in 10. In a few cases, the dose had to be given a second time. Of 7 patients with urticaria, 6 were benefited by treatment with procaine hydrochloride. Durieu and his co-workers,<sup>124</sup> in Brussels, treated 25 patients with asthma with daily intravenous injections of from 5 to 20 cc. of 1 per cent solution of procaine hydrochloride. Lasting improvement was obtained in half the cases and temporary improvement in another 30 per cent. When, however, the asthma was complicated by emphysema and severe bronchitis, only 30 per cent of the patients showed any improvement, and this was only temporary. Appelbaum, Abraham and Sinton<sup>125</sup> describe a boy of 16 with serum disease following the administration of tetanus antitoxin who was relieved within two hours following an intravenous injection of 1 Gm. of procaine hydrochloride in 500 cc. of isotonic solution of sodium chloride. Dressler and Dwork<sup>126</sup> describe a woman of 42 who had had a thoracoplasty for tuberculosis and was treated with large doses of penicillin. In the meantime, 3 Gm. of sulfathiazole crystals had been dusted into her wound after each of the two stages of operation. On the night of the second stage, giant urticaria appeared, and for three days she had a fever, a rash and joint pains. All this, however, was relieved within ten minutes after a slow drip of isotonic solution of sodium chloride (500 cc.) containing 1 Gm. of procaine hydrochloride was started in her vein.

Ephedrine is always useful. Herxheimer<sup>127</sup> does well to point out that whereas small doses, up to 50 mg., may do neither good nor harm,

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122. Brown, E. A.: The Use of Intravenous Ethyl Alcohol in the Treatment of Status Asthmaticus, *Ann. Allergy* 5:193, 1947.

123. State, D., and Wagensteen, O. H.: Procaine Intravenously in Treatment of Delayed Serum Sickness, *J. A. M. A.* 130:990 (April 13) 1946.

124. Durieu, H.; De Clercq, F., and Duprez, A.: Treatment of Asthma with Intravenous Administration of Procaine Hydrochloride, *Acta clin. belg.* 1:150, 1946.

125. Appelbaum, E.; Abraham, A., and Sinton, W.: A Case of Serum Sickness Treated with Procaine Intravenously, *J. A. M. A.* 131:1274 (Aug. 17) 1946.

126. Dressler, S., and Dwork, R. E.: Reactions to Penicillin: Procaine Hydrochloride Intravenously in the Treatment of Reactions Similar to Serum Sickness, *J. A. M. A.* 133:849 (March 22) 1947.

127. Herxheimer, H.: Dosage of Ephedrine in Asthma and Emphysema, *Brit. M. J.* 1:343, 1946.

there are patients who will be benefited if the dose is increased to 100 or even 200 mg., given three or four times a day. He warns, however, that a tolerance to ephedrine is acquired rather quickly, so that intermittent treatment, for not more than three days at a time, followed by two or three days without the drug, is often a satisfactory method of treatment for severe intractable asthma.

*Basic Treatment.*—The concern in the basic treatment of asthma is first of all with the patient as a whole; he needs confidence and reassurance as part of nursing care. The subject was discussed by Rackemann,<sup>128</sup> in 1942, in a paper on the treatment of the asthmatic attack, and now a paper by Carryer and his co-workers<sup>129</sup> from the Mayo Clinic describes a similar point of view. The psychosomatic factors in asthma as part of depletion were discussed in an earlier section. They are always important—so much so that I believe that many of the active types of treatment do good because they provide tangible evidence that something can be done. The treatment of the patient is usually more important than the treatment of his asthma.

*Nonspecific Treatment:* Nonspecific treatment is of various kinds. Cohen and Friedman<sup>130</sup> have used a total of 3 liters of histamine azoprotein ("hapamine") and record their experiences. In 15 cases of urticaria, the results were excellent in 8 and good in 3. In 19 cases of asthma, results were excellent in 8 and good in 1. In other conditions, however, the results were not so good. Dundy, Zohn, and Chobot<sup>131</sup> report on 40 patients, 20 of whom were children. Their results with histamine azoprotein were disappointing. Whereas the drug is supposed to build up a tolerance to histamine, they observed that the reaction to a cutaneous test with histamine, made after the treatment, was the same as that elicited before the treatment was begun.

Godlowski<sup>132</sup> has used insulin shock, giving 20 units of insulin two to three times a week and controlling the severity by feeding dextrose. Eight patients with allergic asthma were treated, and 7 responded with complete recovery, which lasted two and a half years in 1 patient. I wonder what changes in the environment were made at the same time and emphasize again that the results of any treatment in true allergic asthma must be appraised cautiously. In 3 other patients with non-allergic asthma, Godlowski observed no results with insulin shock.

128. Rackemann, F. M.: The Treatment of the Asthmatic Attack, *M. Clin. North America* 26:1501, 1942.

129. Carryer, H. M.; Prickman, L. E.; Maytum, C. K., and Koelsche, G. A.: Treatment of Seriously Ill Asthmatic Patient, *J. A. M. A.* 131:21 (May 4) 1946.

130. Cohen, M. B., and Friedman, H. J.: Histamine Azoprotein in the Treatment of Allergy, *J. Allergy* 18:7, 1947.

131. Dundy, H. D.; Zohn, B., and Chobot, R.: Histamine Azoprotein: Chemical Evaluation, *J. Allergy* 18:1, 1947.

132. Godlowski, Z.: Insulin Shock Treatment of Bronchial Asthma, *Brit. M. J.* 1:717, 1946.

*Mechanical Procedures.*—Mechanical procedures have been devised. At the Johns Hopkins Hospital, Crowe<sup>133</sup> became interested in the treatment for deafness by the removal of the lymphoid tissues in the nasal pharynx by means of radium. At his suggestion the method was tried by Gay<sup>134</sup> in patients with asthma and was found useful, and Ward, Livingston and Moffat<sup>135</sup> report the results in 34 children with asthmatic bronchitis. The lymphoid tissue disappeared in 23 of these 34 children, and, as a result, 15 children were relieved completely of their asthma and 5 others had only occasional mild attacks. The results were good, but they were not perfect, and again I wonder about controls. It is my experience that asthma in children is not too difficult to deal with, since allergy to dusts of various kinds is so often responsible.

*Bronchoscopy:* Bronchoscopy for diagnosis is sometimes useful, particularly when the roentgenogram gives evidence of local areas of collapse. When these areas are located fairly close to the hilus region, bronchoscopy may reveal the cause of the bronchial obstruction and so lead to appropriate treatment. Bronchoscopy for treatment *per se* has been tried, the idea being to remove the tough sticky plugs which occlude the bronchi. The procedure is drastic, and I have seen a patient, a healthy woman in her forties, whose asthma was severe, die on the table with the bronchoscope in place. The preliminary apprehension and the exertion of the procedure increased the difficulty with respiration, until it was more than she could tolerate.

In a recent paper Lell<sup>136</sup> describes the bronchoscopic study of 176 children with asthma. Foreign bodies in the bronchi were seen in 18 and in the esophagus in 5. Other lesions were observed in 23 others. The bronchial mucosa was edematous and engorged, and most of the patients showed a narrowing of the bronchial lumen. In some cases the removal of the pulmonary secretion was life saving.

*Penicillin.*—As soon as penicillin became generally available, in 1944, it was used for asthma. Cooke<sup>87</sup> was one of the first to observe its good effects, and he described several patients with chronic infections of the sinuses and bronchi who were relieved by penicillin injections. Soon after this, Barach<sup>137</sup> began using penicillin in the form of a mist or vapor,

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133. Crowe, S. J.: Local Use of Sulfadiazine Solution, Radon, Tyrothricin and Penicillin in Otolaryngology, *Ann. Otol., Rhin. & Laryng.* **53**:227, 1944.

134. Gay, L. N.: Treatment of Residual Lymphoid Tissue in Nasopharynx by Radium, *J. Allergy* **17**:348, 1946.

135. Ward, A. T., Jr.; Livingston, S., and Moffat, D. A.: Asthma in Children: Treatment with the Radium Nasopharyngeal Applicator, *J. A. M. A.* **133**:1060 (April 12) 1947.

136. Lell, W. A.: Bronchoscopy as Aid in Diagnosis and Treatment of Allergic Pulmonary Disease, *Arch. Otolaryng.* **43**:49 (Jan.) 1946.

137. Barach, A. L.: Penicillin Aerosol and Negative Pressure in the Treatment of Sinusitis, *Am. J. Med.* **1**:268, 1946.



which could be inhaled. Since then, penicillin, given by injection or in the form of an aerosol, has been used by numerous workers in pulmonary disease of every kind, and on the whole the results have been good. In a comprehensive article written in 1945, Vermilye<sup>138</sup> reviewed the literature; he described the technic by which a small amount of concentrated penicillin solution (50,000 units per cubic centimeter) was placed in a "vaponephrin" nebulizer, so arranged that a pressure of oxygen would flow through the nebulizer whenever the patient put his finger on the end of the open Y on the tube connection. It is important that the patient learn to correlate the flow of penicillin vapor with his own inspiration. In all sorts of acute and chronic infections of the bronchi and lungs, penicillin aerosol has been tried and observed to be effective in a large proportion of the cases. Segal and Ryder<sup>139</sup> in Boston have used much the same apparatus. In pneumonia the results are good; in bronchiectasis and pulmonary abscess the patients are benefited, but not cured. In "infective bronchial asthma" the treatment was given to 22 patients in courses lasting from three days to three weeks. No figures are given in the latest paper, but a sentence reads: "This therapy was generally disappointing, although striking improvement was occasionally observed." In the 6 cases of pulmonary emphysema the results were excellent. Segal used 1 cc. of a solution containing 25,000 units of calcium or sodium penicillin, which is placed in the "vaponephrin" atomizer and blown through with oxygen pressure. Blood levels ranging from 0.15 up to 0.225 units per cubic centimeter were obtained, but, as expected, these levels fell to 0 within two hours. Treatment with penicillin must be repeated frequently.

In his paper, Barach<sup>137</sup> has summarized his results with treatment of sinusitis with penicillin aerosol. A total of one hundred and twenty-two courses of treatment was given to 110 patients—some with acute and most with chronic sinusitis—and the protocol indicates that at least half of them had asthma. Unfortunately, the ages of these patients are not given, nor is there any statement concerning the kind of asthma which they had. One would like to assume that most of these patients were older persons, with the kind of asthma which is of intrinsic origin and associated with polypoid sinusitis. With one hundred and twenty-two courses, decided improvement was obtained in 39 cases—about 30 per cent—and moderate improvement was obtained in another 43 cases, or 35 per cent, on the whole a good showing. In the "good" group, roentgenograms of the sinuses taken before and after treatment showed virtual clearing in about half the cases, and cultures taken before and

138. Vermilye, H. N.: *Aerosol Penicillin in General Practice*, J. A. M. A. **129**:250 (Sept. 22) 1945.

139. Segal, M. S., and Ryder, C. M.: *Penicillin Inhalation Therapy*, New England J. Med. **236**:132, 1947.

after treatment showed a striking change. In 24 of 41 cases in which cultures were made, all gram-positive organisms were cleared entirely with the penicillin aerosol, leaving behind the gram-negative organism. Southwell,<sup>140</sup> in England, had a smaller series of patients—43 in all—but they included 17 with “chronic bronchitic asthma.” Of these, I was cured and 13 were improved with the penicillin inhalations. Four patients with asthma were treated, but without results. Whereas the technic involving a fancy nebulizer and an oxygen tank is rather difficult, Morse,<sup>141</sup> a “country doctor” in Nova Scotia, has pointed out that a simple penicillin spray can be obtained easily with a “DeVilbiss no. 15” atomizer, activated by a hand bulb. He dissolves 100,000 units of penicillin in 10 cc. of sterile water and places the whole solution in the atomizer chamber. The patient is instructed to squeeze the bulb during every inspiration for ten minutes every hour and then after four treatments to repeat for ten minutes once every four hours while awake. This simple method was used by Dr. Morse for the treatment of all sorts of pulmonary disease, and he obtained good results with it. Fincke<sup>142</sup> also has a simple method; he suggests that a bicycle pump gives abundant air under sufficient pressure and with little effort, and if the pump is in good condition the spray can be activated through several inspirations with only one down stroke.

In the meantime, penicillin given by injection, as used originally by Cooke, may still be important. Leopold<sup>143</sup> advised that 40,000 units be injected at intervals of four hours, to total 240,000 units a day. He used the method in 85 cases of asthma, in 62 of which the disease was of the perennial intrinsic type and 20 of the allergic type. Unfortunately, the results were not good. The wheeze was decreased in 26 patients, or 41 per cent, but only 10 patients, or 16 per cent, enjoyed any continued improvement. For secondary infections in asthma, as in many other conditions, penicillin is useful, but the fact that penicillin does not always produce striking benefit in patients with asthma is in itself some argument that an infection is not the primary cause of trouble. It is my opinion that treatment with penicillin in all forms should be reserved for those cases in which the evidence of active infection is good.

*Reactions to Penicillin.*—Reactions to penicillin do occur, the commonest being urticaria, of the serum sickness type, which, like the reaction to serum itself, develops after an interval of several days and runs a

140. Southwell, N.: Inhaled Penicillin in Bronchial Infections, *Lancet* 2:225, 1946.

141. Morse, F. W.: Penicillin Spray by Bulb Atomizer in Respiratory Infections, *J. A. M. A.* 132:272 (Oct. 5) 1946.

142. Fincke, W.: Simplification of Penicillin Aerosol Therapy for Home Treatment, *Am. Pract.* 1:643, 1947.

143. Leopold, H. C.: Penicillin Therapy in Chronic Bronchial Asthma, *J. Allergy* 17:166, 1946.

rather similar course. Figures for the incidence are quoted by Gordon<sup>144</sup> as follows: Keefer observed urticarial reactions in 14 of 500 patients, or 2.9 per cent. Lyons observed them in 12 out of 209 patients, or 5.7 per cent, Moore in 8 out of 1,418, or 0.56 per cent, and Stokes in only 2 out of 192 patients (1.2 per cent). Romansky<sup>145</sup> reports allergic reactions, mostly urticaria and angioneurotic edema, in 5 per cent of 600 patients treated with intramuscular injections of calcium penicillin in wax and peanut oil. Most of them occurred on the fourth day.

How can one tell whether a given patient is sensitive or not—whether a reaction will occur? Callaway and Barefoot<sup>146</sup> made studies in 5 patients who had experienced urticaria following penicillin therapy. Cutaneous tests were made by the intracutaneous and passive transfer methods, and precipitin tests were made, but none of these laboratory procedures gave positive results. In a general article on allergy to drugs, Sherman<sup>147</sup> declares that the reaction neither to cutaneous tests nor to passive transfer with the Prausnitz-Kustner technic is a reliable index of penicillin sensitivity. On the other hand, Peck and Siegal<sup>148</sup> observed a positive reaction to a cutaneous test in a man of 63 in whom a diffuse eruption developed after parenteral administration of penicillin, and when the lesions subsided the second dose of penicillin elicited the reaction once more. After that small doses of penicillin were given at frequent intervals and desensitization was finally accomplished, so that the effective dosage, which the man needed, could be given.

As in other allergies to drugs, the best method of prevention of reaction is in the physician's thinking of allergy and then asking two questions: First: "Have you ever had hay fever, asthma or peculiar reactions?" That is to say: "Is this patient an allergic person with the asthmatic state? Second, "Have you ever been given this drug before, and if so did the dose disturb you in any way?" In other words: Has this patient been sensitized?

Local sensitiveness to penicillin may develop when it is used locally in sprays, nose drops or ointments. Hopkins and Lawrence<sup>149</sup> observed that penicillin ointment produced local sensitiveness of the skin, as de-

144. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, *J. A. M. A.* **131**:727 (June 29) 1946.

145. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, *Am. J. Med.* **1**:395, 1946.

146. Callaway, J. L., and Barefoot, S. W.: Immunological Studies on Patients Developing Urticaria Associated with Penicillin Therapy, *J. Invest. Dermat.* **7**:285, 1946.

147. Sherman, W. B.: Drug Allergy, *Am. J. Med.* **3**:586, 1947.

148. Peck, S. M., and Siegal, S.: Successful Desensitization in Penicillin Sensitivity, *J. A. M. A.* **134**:1546 (Aug. 30) 1947.

149. Hopkins, J. G., and Lawrence, H.: Sensitization to Penicillin, *J. Allergy* **18**:251, 1947.

terminated by positive reactions to patch tests, in 13 per cent of the patients treated. Goldman and Mason<sup>150</sup> treated 350 patients with penicillin ointment and observed that reactions to patch tests were positive in 134, or 38 per cent. In 1 of the patients there developed generalized exfoliative dermatitis. Cormia and his co-workers<sup>151</sup> have shown that in animals penicillin shows all the characteristics of a good allergenic substance. Single doses of commercial penicillin sensitize guinea pigs, so that the uterus reacts well in the Dale bath.

#### ALLERGY TO DRUGS IN GENERAL

There are two papers which deal with allergy to drugs in its broad aspects. Sherman's<sup>147</sup> paper has been noted. He describes the symptoms, the mechanism and the methods of diagnosis in detail.

In his article, Dragstedt<sup>152</sup> points out that certain "idiosyncrasies" may not be allergic: the mechanism may depend on other factors. In rats, for example, sulfathiazole inhibits folic acid and so leads to granulocytopenia. Reactions to neoarsphenamine can be reduced or prevented by treatment with ascorbic acid, which inhibits the oxidation of the drug and so prevents the formation of toxic breakdown products. The polyneuritis, which results sometimes from treatment with sulfonamide drugs, may depend on a deficiency of vitamin B<sub>1</sub>, which predisposes the tissue to injury by drugs. Dragstedt sets up provisional criteria for the diagnosis of allergy to drugs as follows:

1. The reaction pattern must be consistent with allergic manifestations; it must include urticaria, asthma, rhinitis or dermatitis.

2. There should be a history of a primary or sensitizing dose followed by an interval, and the reaction should follow promptly when the new treatment is given.

3. Treatment with epinephrine and other sympathetic stimulants should relieve the symptoms, as they do in more typical allergy.

*Sulfonamide Drugs.*—The sulfonamide drugs are important sensitizers, and the cause of many allergic reactions due to drugs. Local treatment with the sulfonamide drugs, in the form of wet dressings or ointments, appears to be particularly important. Sulzberger and his co-workers<sup>153</sup> experimentally produced small burns, about 1 cm. in diameter,

150. Goldman, L.; Friend, F., and Mason, L.: Dermatitis from Penicillin, *J. A. M. A.* **131**:883 (July 13) 1946.

151. Cormia, F. E.; Lewis, B. M., and Hoppe, M. E.: Experimental Aspects of Penicillin Sensitization: II. With Reference to the Schultz-Dale Phenomenon, *J. Invest. Dermat.* **8**:395, 1947.

152. Dragstedt, C. A.: Idiosyncrasy to Drugs, *J. A. M. A.* **135**:133 (Sept. 20) 1947.

153. Sulzberger, M. B.; Kanof, A.; Baer, R. L., and Lowenberg, C.: Sensitization by Topical Application of Sulfonamides, *J. Allergy* **18**:92, 1947.

in the skin of normal persons and then treated these burns with various sulfonamide preparations. In all, 264 men were subjected to the experiment. Of these, 49 were treated with a 5 per cent sulfadiazine cream, and of this number, 57 per cent experienced localized dermatitis on the treated spot. With other sulfonamide creams the incidence was much smaller, and the authors demonstrated that the sensitizing potentials corresponded rather accurately to the degree of solubility of the drug in water. Two factors were important. The skin must be damaged before the ointment is applied, and previous exposure to the drug materially increased the number and severity of reactions obtained.

Dowling, Hirsh and Lepper<sup>154</sup> observed that the patient who had previously experienced fever, dermatitis or conjunctivitis from a reaction to drugs was likelier than some other person to experience a similar reaction during subsequent treatment. Among 48 patients to whom the same sulfonamide drug was given another time, 33, or 69 per cent, experienced toxic reactions, but, among 30 other patients who received a different sulfonamide drug, only 5, or 17 per cent, reacted. Sherman and Cooke<sup>155</sup> observed positive reactions to cutaneous and passive transfer tests in a woman sensitive to sulfadiazine, but no such reaction in 2 other patients.

*Influenza Vaccine.*—Reactions to influenza, yellow fever and perhaps to typhus vaccine are being noted with the increasing use of these preparations. Stull<sup>156</sup> has observed that the chick embryo yolk sac vaccines do contain sufficient egg protein to cause severe systemic reactions if given to persons sensitive to eggs. Ratner and Untracht,<sup>157</sup> on the other hand, observed that whereas 10.2 per cent of 108 allergic children were sensitive to egg, only 4.6 per cent were sufficiently sensitive to make the treatment dangerous. The paper contains a full discussion. Curphey<sup>158</sup> describes the fatal reaction which followed an injection of influenza A and B vaccine in a young girl aged 3½ years. Four hours later the child had pain in her stomach, chills, vomiting and a temperature of 109 F.

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154. Dowling, H. F.; Hirsh, H. L., and Lepper, M. H.: Toxic Reactions Accompanying Second Courses of Sulfonamides in Patients Developing Toxic Reactions During a Previous Course, *Ann. Int. Med.* **24**:629, 1946.

155. Sherman, W. B., and Cooke, R. A.: Sulfadiazine Sensitivity with Demonstrable Skin-Sensitizing Antibody in the Serum, *Am. J. Med.* **11**:588, 1947.

156. Stull, A.: Allergenic and Anaphylactogenic Properties of Vaccines Prepared from Embryonic Tissues of Developing Chicks: III. A Study to Determine Whether Chick-Embryo Yolk-Sac Vaccines Contain Sufficient Egg Proteins to Cause Severe Systemic Reactions if Given to Egg-Sensitive Individuals, *J. Immunol.* **53**:343, 1946.

157. Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, *J. A. M. A.* **132**:899 (Dec. 14) 1946.

158. Curphey, T. J.: Fatal Allergic Reaction Due to Influenza Vaccine, *J. A. M. A.* **133**:1062 (April 12) 1947.

(by rectum). In the hospital cyanosis and convulsions developed, and she died in seven hours, despite treatment with oxygen, epinephrine and bleeding. The autopsy did not reveal that death was due to anaphylaxis. The lungs showed an early pneumonic reaction, which was comparable, perhaps, to the Schwartzman phenomenon. Rifkin<sup>159</sup> reports the death of a man aged 24 about twenty-five minutes after the injection of 1 cc. of typhus vaccine. In his case there was a history of previous sensitiveness to egg, and autopsy showed the characteristic emphysema of anaphylaxis. Rubin<sup>160</sup> reports a soldier who had hay fever and had been sensitive to eggs all his life. After a dose of yellow fever vaccine, prepared from infected chick embryos and typhus vaccine prepared from infected yolk sacs, angioneurotic edema and asthma developed.

*Iodopyracet* ("Diodrast").—Allergic reactions to drugs may result from preparations used in diagnosis as well as in treatment. Reactions to iodopyracet injection ("diodrast"), used for roentgenograms of the kidney, are not uncommon. Alyea and Haines<sup>161</sup> present some interesting figures concerned with the use of iodopyracet in 1,675 cases. Reactions to cutaneous tests made on all of these were positive in 15 per cent. Of the subjects with positive cutaneous reactions, only 16 per cent showed any systemic reaction when the drug was injected. Moreover, in the subjects with negative reactions to the cutaneous test, systemic reactions occurred in 4 per cent. Discrepancies occurred in both directions. When the patient was also allergic, reactions to cutaneous tests with iodopyracet occurred in a larger percentage. As expected, these patients showed their capacity for development of sensitiveness to foreign substances. More recently I have heard that a better test for sensitivity to iodopyracet consists in injecting intravenously 1.0 cc. of a 1 to 20 dilution of the material which is to be used undiluted later. If the patient is sensitive, the small dose will produce a reaction and give the warning.

*Congo Red*.—Congo red used for the study of amyloid disease can cause systemic reaction after intravenous administration. Selikoff and Bernstein<sup>162</sup> observed 100 consecutive cases, with severe systemic reactions in 6 cases and death in 2.

*Iodized Oil*.—Iodized oil used in bronchoscopy is another offender.

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159. Rifkin, H.: Death Due to Administration of Typhus Vaccine, *Ann. Int. Med.* 25:346, 1946.

160. Rubin, S. S.: Allergic Reaction Following Typhus Fever Vaccine and Yellow Fever Vaccine Due to Egg Yolk Sensitivity, *J. Allergy* 17:21, 1946.

161. Alyea, E. P., and Haines, C. E.: Intradermal Test for Sensitivity to Iodopyracet Injection, or "Diodrast," *J. A. M. A.* 135:25 (Sept. 6) 1947.

162. Selikoff, I. J., and Bernstein, I. J.: Systemic Reactions to the Intravenous Administration of Congo Red, *Quart. Bull., Sea View Hosp.* 8:131, 1946.

Mahon<sup>163</sup> found 10 cases in the literature and adds the report of a man who received 10 cc. of "lipiodol" (iodized poppy seed oil 40 per cent) in each lung; twenty minutes later convulsions developed, and he died. His tracheobronchial tree was observed to be completely filled with sticky mucus.

*Drugs Used for Treatment.*—These drugs are often more important. Thiouracil may produce granulocytopenia. Morton<sup>164</sup> reviewed 59 cases reported in the literature and added 2 more. Reingold and Webb<sup>165</sup> treated a young woman with intravenous injections of thiamine hydrochloride. The first dose of 100 mg. caused an immediate burning sensation and sweating, but it passed. Three days and twenty days later, respectively, the second and third doses produced no symptoms, but the fourth dose, given on the thirty-fifth day, caused immediate dyspnea, with cyanosis and death. Nicotinic acid ("niacine") is injected occasionally for severe vitamin deficiency or because of its vasodilating action. Perner<sup>166</sup> reports 2 patients who suffered severe systemic disturbances after relatively small doses. Livingston and Livingston<sup>167</sup> report another case of granulocytopenia and jaundice after treatment with propylthiouracil (a thiourea derivative). Agress<sup>168</sup> reports reactions to quinacrine hydrochloride ("atabrine")—5 cases among Chinese soldiers, which represents one reaction in every 2,000 or 3,000 cases. Each soldier experienced severe exfoliative dermatitis and hepatitis, beginning on the second or sometimes the tenth day. Four of the 5 soldiers gave positive reactions to patch tests with quinacrine hydrochloride; all had eosinophilia, and 3 of the 5 died. Wright, Doan and Haynie<sup>169</sup> describe a student of 22 who sprayed his room with an aerosol bomb containing dichlorodiphenyltrichloroethane (D D T). Ten days later sore throat developed, and he was observed to have a white cell count of only 3,800 with only 1 polymorphonuclear cell in the smear. Fortunately,

163. Mahon, G. S.: Reaction Following Bronchography with Iodized Oil, *J. A. M. A.* **130**:194 (Jan. 26) 1946.

164. Morton, J. H.: Agranulocytosis Caused by Thiouracil: A Review of Fifty-Nine Cases in the Literature and a Report of Two Additional Cases, *Am. J. Med.* **2**:53, 1947.

165. Reingold, I. M., and Webb, F. R.: Sudden Death Following Intravenous Injection of Thiamine Hydrochloride, *J. A. M. A.* **130**:491 (Feb. 23) 1946.

166. Perner, L.: Anaphylaxis to the Injection of Nicotinic Acid (Niacin): Successful Treatment with Epinephrine, *Ann. Int. Med.* **46**:290, 1947.

167. Livingston, H. J., and Livingston, S. F.: Agranulocytosis and Hepato-cellular Jaundice: Toxic Reactions Following Propylthiouracil Therapy, *J. A. M. A.* **135**:422 (Oct. 18) 1947.

168. Agress, C. M.: Atabrine as a Cause of Fatal Exfoliative Dermatitis and Hepatitis, *J. A. M. A.* **131**:14 (May 4) 1946.

169. Wright, C. S.; Doan, C. A., and Haynie, H. C.: Agranulocytosis Occurring After Exposure to a D.D.T. Pyrethrum Aerosol Bomb, *Am. J. Med.* **1**:562, 1946.

the prompt injection of penicillin prevented the development of an infection of the respiratory tract. It is extraordinary that foreign serum is still being used from time to time, and with little attention to its dangerous possibilities. From England comes the report of Gardner<sup>170</sup> describing the physician who was called to see a small boy who had crushed his hands. By telephone he ordered the immediate injection of 3,000 units of tetanus antitoxin. Almost at once the boy complained of feeling ill, and in an hour he was dead. No questions had been asked about previous administration of horse serum, and no thought had been given to the possibility of allergy.

Finally, Friedlaender and Feinberg<sup>171</sup> discussed the problem of allergy to acetylsalicylic acid—a clinical factor which is of considerable practical importance in certain patients with asthma. The allergy to acetylsalicylic acid denotes a severe type of asthma. The condition is typical of allergy to drugs. Cutaneous tests with acetylsalicylic acid elicit no reaction, and so far there is no way except that of clinical trial for recognizing the condition. Feinberg adds: "If aspirin sensitiveness can develop in this insidious manner, why cannot the patient be sensitive to any number of other substances non-protein in nature?" It is a troublesome thought.

*Chase's Work on Drug Allergy.*—The work done by Landsteiner has been continued by Chase. Chase<sup>172</sup> gives evidence that the sensitization of animals with simple chemical compounds is, in fact, mediated by an antibody mechanism which is comparable to that seen in more ordinary allergy. Chase inoculated guinea pigs intradermally with a series of doses of a chemical given four or five days apart over a period of five to twelve weeks. He observed that toward the end of treatment the serum of the animal was able to transfer the reaction capacity to the skin of a normal recipient guinea pig. When the cutaneous sites of these recipient animals were tested with the original chemical, reactions of the immediate urticarial type, often with pseudopods, were observed. These reactions were highly specific. Thus, if the sensitizing serum was obtained from an animal prepared by painting with picryl chloride, the reaction in the recipient animal could be elicited only with that drug; the recipient showed no reaction when the site was tested, for example, with orthochlorobenzylchloride. In another experiment Chase could demonstrate that the sensitive serum was active enough to produce typical passive anaphylaxis in a recipient animal. By this work, Chase has dem-

170. Gardner, E.: Rapid Death Following Injection of Antitetanic Serum. *Lancet* 1:689, 1946.

171. Friedlaender, S., and Feinberg, S. M.: Aspirin Allergy: Its Relationship to Chronic Intractable Asthma, *Ann. Int. Med.* 26:734, 1947.

172. Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: X. Antibodies Inducing Immediate-Type Skin Reactions, *J. Exper. Med.* 86:489, 1947.



onstrated that the antibodies involved in allergy to drugs, particularly in that type of allergy which has been called contact dermatitis, the antibodies are of the same type as those seen in typical anaphylaxis. The allergens used here are "poor" allergens. Nevertheless, when the experimental animals are treated long enough, antibodies develop and reactions occur the same as when other animals are treated with "good" allergens, like egg white or horse serum. As Chase points out, immediate urticarial wheal and erythema reactions to cutaneous tests are seen occasionally in patients with allergy to drugs. He notes Kern's patients sensitive to phthalic anhydride, Feinberg and Watson's patient sensitive to dichloramine T. and Sherman and Cooke's patients sensitive to sodium sulfadiazine; all these are authentic cases. Whereas such reactions are rare, the fact that they occur at all in the clinic confirms the principles which Chase has now demonstrated in the laboratory.

In another paper, Chase<sup>173</sup> has pointed to another mechanism which has a possible clinical bearing. When his experimental animals receiving treatment with a series of intradermal doses of a drug, like dinitrochlorobenzene, were fed by mouth a small quantity of the same chemical, the demonstration of sensitiveness did not occur. The treatment given beforehand had induced a state of resistance against subsequent experimental cutaneous sensitization by the same substance.

The whole concept of allergy to drugs is interesting, partly because of the difficulty in diagnosis, but more because the sensitiveness is directed to substances which are not proteins; they are simple chemical compounds. Occasionally the reactions to cutaneous tests are positive, but the discrepancies between the positive reactions to cutaneous tests and the subsequent systemic reactions are rather disconcerting. With respect to iodopyracet, even when the reaction to the cutaneous test is positive, the intravenous injection may proceed without difficulty, and then in other cases when the reaction is completely negative the subsequent injection causes trouble. The whole problem of allergy to drugs is of great practical importance, and it needs much further study.

#### HAY FEVER

The recent literature on hay fever has been reviewed by Kaplan,<sup>174</sup> and only a few points need be mentioned here. New pollen surveys appear from time to time; they are essential, for no physician can treat hay fever without understanding the pollens in his own environment.

173. Chase, M. W.: Inhibition of Experimental Drug Allergy by Prior Feeding of the Sensitizing Agent, *Proc. Soc. Exper. Biol. & Med.* **61**:257, 1946.

174. Kaplan, M. A.: Progress in Allergy: Hay Fever; a Review of the Literature of 1946, *Ann. Allergy* **5**:253, 1947.

Clinical studies on hay fever are interesting. Brown and his co-workers<sup>175</sup> observed that 26 out of 38 pollen-sensitive persons showed a diminished vital capacity during the pollen season, even though they were free of asthma at the time the measurements were made. Rackemann<sup>176</sup> demonstrated that the level of pollen tolerance is of practical importance in the treatment of hay fever. The level at which systemic reactions can be produced by excessive treatment remains fairly constant for each patient. Doses just below this reaction level can be given without danger, and doses near that level will do good. The concept of an optimal zone of treatment dosage is confirmed. Alexander and Johnson<sup>177</sup> have compared the concentration of ragweed antibodies with circulating antigens and compared these two with the symptoms and the results of treatment. It is interesting to see pollen antigens and circulating pollen antibodies occurring together; one would expect them to precipitate each other out of solution. It is not clear why this does not happen. As for the results of treatment, they bear little relation to the laboratory observations.

Molds are more interesting than pollens, if only because the whole problem of molds is so complex. Bieberdorf and Hampton<sup>178</sup> made a twelve months' survey of air-borne molds in San Antonio, Texas. *Hormodendron* and *Alternaria* were commoner than other molds. Of 186 patients who reacted to tests with molds, all but 6 gave a history compatible with sensitiveness to molds. In contrast, Blumstein<sup>179</sup> observed that 41 of 101 patients reacted to one or more of thirteen mold extracts, but that only 12 of these 41 were clinically sensitive. Fraenkel<sup>180</sup> studied 522 patients with asthma in England and observed 84 who gave positive reactions to cutaneous tests with molds. Hyde and Williams<sup>181</sup> present graphs of the pollens and molds observed in the air over Eng-

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175. Brown, E. A.; Nobili, C.; Sannella, T., and Wadsworth, G. P.: Dyspnoea and Diminished Vital Capacity as a Symptom and a Sign in Hay Fever. *Dis. of Chest* **12**:205, 1946.

176. Rackemann, F. M.: Pollen Tolerance: Its Bearing on the Treatment of Hay Fever, *J. Allergy* **18**:164, 1947.

177. Alexander, H. L.; Johnson, M. C., and Alexander, J. H.: Measurement of Circulating Ragweed Antibodies and Antigen: Correlation with Symptoms and Treatment, *J. Allergy* **17**:340, 1946.

178. Bieberdorf, F. W., and Hampton, S. F.: Airborne Fungi in Allergic Disease: II. Survey of Airborne Fungi in San Antonio, Texas, Area; Incidence of Skin Reactions with Mold Extracts, *Ann. Allergy* **4**:23, 1946.

179. Blumstein, G. I.: Mold Allergy: II. Clinical Analysis, *Ann. Allergy* **3**:341, 1945.

180. Fraenkel, E. M.: Bronchial Asthma and Mold Fungus Allergy, *Schweiz. med. Wchnschr.* **77**:115, 1947.

181. Hyde, H. A., and Williams, D. A.: A Daily Census of *Alternaria* Spores Caught from the Atmosphere at Cardiff in 1942 and 1943, *Tr. Brit. Mycol. Soc.* **29**:78, 1946. *Studies in Atmospheric Pollen: I. A Daily Census of Pollens at Cardiff (Wales) 1942*, *New Phytologist* **43**:49, 1944.

land. *Alternaria* is common; it reaches sharp peaks in August and September each year.

The difficulty with all these reports is that molds occur not only in many genera, but in hundreds of species within each genus. The problem of specificity among these species has been shown by the "Guba" experiment, in which Rackemann and his co-workers<sup>182</sup> demonstrated that 3 patients were sensitive specifically to one particular species in the *Cladosporium* genus. Cutaneous tests with related species using extracts prepared in precisely the same manner elicited essentially negative reactions. If this process of mold specificity is widespread, how shall one cope with it? Is it any wonder that the literature concerning allergy to molds is so difficult to deal with?

#### ECZEMA

The consideration that the kind of eczema which occurs in infancy and in young persons, which involves the face, neck and cubital and popliteal spaces and is called "flexural eczema," "neurodermite" or "atopic eczema," may be due to disturbances in fat metabolism is not new, but in recent years interest in it has been rearoused. In 1929 and 1930, Burr and Burr<sup>183</sup> published two papers on the effects of a rigid exclusion of all fat from the diet of rats. They observed that the unsaturated fatty acids, especially linolic and arachidonic acids, were essential for growth and reproduction in rats, but, more important, these elements were necessary for the nutrition and the integrity of the skin of the animals. Without these fatty acids the skin became dry and scaly and the hair became coarse and scanty.

In 1933, Hansen<sup>184</sup> observed that in certain patients with infantile eczema there were changes in the serum lipids, and he claimed that the feeding of fats was of benefit. In 1941, Finnerud and his assistants<sup>185</sup> took up the problem and confirmed the fact that the feeding of lard was useful in eczema. In the next year, Burr<sup>186</sup> wrote a comprehensive review of the subject, presenting the photographs of an infant with severe eczema before treatment and with clear skin after the administration of

182. Rackemann, F. M.; Randolph, T. G., and Guba, E. F.: The Specificity of Fungous Allergy, *J. Allergy* 9:447, 1938.

183. Burr, G. O., and Burr, M. M.: A New Deficiency Disease Produced by Rigid Exclusion of Fats from Diet, *J. Biol. Chem.* 82:345, 1929; On Nature and Role of Fatty Acids Essential to Nutrition, *ibid* 86:587, 1930.

184. Hansen, A. E.: Serum Lipid Changes and Therapeutic Effects of Various Oils in Infantile Eczema, *Proc. Soc. Exper. Biol. & Med.* 31:160, 1933.

185. Finnerud, C. W.; Kesler, R. L., and Wiese, H. F.: Ingestion of Lard in Treatment of Eczema and Allied Dermatoses: Clinical and Biochemical Study, *Arch. Dermat. & Syph.* 44:849 (Nov.) 1941.

186. Burr, G. O.: Significance of the Essential Fatty Acids, *Federation Proc* 1:224, 1942.

2 or 3 teaspoonfuls of lard each day for a month. He describes the observation of low iodine numbers, which indicate that the amount of unsaturation of the serum lipids is at a low level. The scaly skin of calves, chicks and dogs which developed when fat was restricted was accompanied with low iodine indexes of the blood serum, and similar results were seen in eczema. Fats have a sparing action on other food elements, especially on pyridoxine (vitamine B<sub>6</sub>), as well as on vitamin A. The nutritive function of the fatty acids affects the kidneys, as well as the skin. In the meantime di Sant'Agnese and Larkin<sup>187</sup> observed that the absorption of vitamin A was impaired in 4 patients with severe eczema who also had severe eosinophilia—with up to 25 and 35 per cent of eosinophils—and severe malnutrition.

More recently three new and good papers have been published. Hansen and his co-workers<sup>188</sup> observed 225 patients with eczema. Studies of the serum lipids were made in 171 patients, mostly infants and children, and the iodine index was observed to be below the mean value for normal persons of the same age. When lard, in doses of 4 teaspoonfuls a day, was fed to 148 of these children, the clinical response was good in 60 (40 per cent) and fair in 51, or 35 per cent, and in these improved patients the iodine indexes became larger, in proportion to the degree of improvement. The authors add, however, that in patients treated with coal tar, with a change in diet, that the iodine indexes also showed a rise. Frazier and Small<sup>189</sup> present a comprehensive study of all "eczema," the relation to allergy and the biochemistry of cutaneous lesions in general. Vesicants, like the arsenic compounds, are harmful, because once having penetrated the outer keratin layer, or having reached the skin through the blood stream, they interfere with various tissue enzymes, so that they disturb the normal process by which sugar and other foods are absorbed by the cells of the skin. They suggest that in eczema the disturbed lipid metabolism of the skin interferes with nutrition of the skin and causes trouble. Stoesser<sup>190</sup> notes that soy beans contain unsaturated fatty acids and that soy bean milk is good for children with eczema. He treated 31 patients with soy bean milk and observed the iodine indexes to be low at the start of treatment and much higher later. In the discussion of Stoesser's paper, it was pointed out that fever improves eczema and

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187. di Sant'Agnese, P. A., and Larkin, V. deP.: Vitamin A Absorption in Infantile Eczema, *Proc. Soc. Exper. Biol. & Med.* **52**:343, 1943.

188. Hansen, A. E.; Knott, E. M.; Wiese, H. F.; Shaperman, E., and McQuarrie, I.: Eczema and Essential Fatty Acids, *Am. J. Dis. Child.* **73**:1 (Jan.) 1947.

189. Frazier, C. N., and Small, A. A.: Allergic Dermatitis: A View of Its Immunologic and Biochemical Implications, *Am. J. Med.* **3**:571, 1947.

190. Stoesser, A. V.: Influence of Soy Bean Products on the Iodine Number of the Plasma Lipids and the Course of Eczema, *J. Allergy* **18**:29, 1947.

that at the same time this fever lowers the iodine index. The discrepancy is difficult to explain, unless there be a mobilization of lipids in the skin at the expense of those in the circulating blood, but there is no support for this belief.

In the winter of 1947-1948 my associates and I observed 4 patients with "atopic eczema" or "neurodermatitis" who were virtually "cured" after taking 4 tablespoonfuls of lard, either cold and used like butter on bread or warm and liquid and poured onto bread, potato or vegetables. The improvement began in a few days, and the skin was clear within two weeks. Needless to say, the same treatment for other patients has had no such beneficial effect. Does this mean that there are different types of cases: those in which there is and those in which there is not response to unsaturated fatty acid? A carefully made clinical study might answer the question and help to explain the doubts and the discrepancies in the literature.

In the meantime, Engman and MacCardle<sup>191</sup> have declared that in albino rats fed on a diet deficient in magnesium lesions developed similar to those of neurodermatitis. So far no one has paid attention to the possibility of a deficiency of something else besides unsaturated fatty acid in eczema in human beings, and that is a challenging thought.

#### SUMMARY AND CONCLUSIONS

This review describes progress in several directions. The concept of an "asthmatic state" as a constitutional factor, which explains the tendency in predisposed persons to development of one or other of the allergic diseases, as apposed to some other chronic disturbance, would appear to be supported. In more than half of this group, the antigen-antibody mechanism of allergy provided the exciting cause for the production of symptoms. In the other half, however, the exciting cause was not allergy: the causes included infections, and depletion, the latter resulting from stress and strain of various kinds of the soma or of the psyche.

The theory that each of these exciting factors liberates a poison (H substance) which is directly responsible for the symptoms appears necessary from the clinical point of view, and with respect to the antigen-antibody reaction, the evidence in human beings as well as in animals, shows that histamine is at least an important element in the poison. In the cases of infections and of depletion, the evidence that histamine is released is not too clear, but, at least, it is known that other factors besides the antigen-antibody reaction can release this histamine.

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191. Engman, M. F., Jr., and MacCardle, R. C.: A New Approach to the Problem of a Disseminated Neurodermatitis, *Arch. Dermat. & Syph.* **46**:337 (Sept.) 1942.

Selye's discussion of the "diseases of adaptation" appears to have an important and direct bearing on this subject.

The term "release," as applied to histamine, is good, for there is real evidence that this substance is present in many cells and tissues of the body and can move from its bound state in the tissues into an unbound state in the blood plasma. As Rose has explained, this movement can be demonstrated in a number of laboratory experiments. So far, however, it is not known how extensively it occurs in patients with asthma or urticaria, and the question needs study. It has now become clear that measures of the total histamine, which include both its bound and its free forms, are not helpful to the understanding of the process.

The fact that the antihistaminic drugs, which are so effective in neutralizing histamine when tested in direct experiment, are not more effective in the treatment of all allergic diseases has two implications: First, the discrepancy confirms the suspicion that histamine, by itself, does not constitute all of the mediating poison, and, second, the variation in the effect of the drugs suggests that not all of the clinical manifestations of allergy have precisely the same basic mechanism.

The pathologic aspects of the allergic diseases is understood better than it has previously been, thanks largely to the work of Rich, and as a result, attention has been directed to studies of the blood vessels, on the one hand, and to studies of the connective tissue, the collagen, on the other. The lesions observed in experiments with foreign serum in animals, as well as those seen in patients at autopsy, has led to a much wider appreciation of the mechanisms of allergy in clinical medicine as well as to a broader concept of allergy itself. The fact that Selye could produce lesions of similar, if not identical, character by treating his animals with adrenocortical steroids is in accord with the concept that stress and strain (depletion) is sufficient to explain the symptoms.

With even greater assurance, I can repeat that, "all is not allergy that wheezes" and can say, with equal assurance, that in many cases "the treatment of the patient is more important than the treatment of his disease."

Dr. Bram Rose of Montreal and Dr. Anne Forbes of Boston gave suggestions in the preparation of this paper.

## GASTROENTEROLOGY

A Review of the Literature from July 1946 to July 1947

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*Concluded from page 598*

### SMALL INTESTINE

*Motility.*—In studies by Cantoni and Eastman<sup>304</sup> on the responsiveness of the isolated guinea pig intestine, maximal contractions obtained in response to a large dose of histamine, acetylcholine, pilocarpine, barium chloride and "mecholy chloride" were followed by temporary depression. On the other hand, a maximal contraction in response to large doses of potassium chloride did not result in a decreased contractility. A small increase in the potassium-calcium ratio of the perfusion fluid, such as is obtained by doubling the potassium content of Tyrode solution, was sufficient to neutralize the effect of large doses of histamine, acetylcholine, pilocarpine and barium chloride.

B-dimethylaminoethyl benzilate hydrochloride abolished the activity of exteriorized loops of dog intestine to a degree commensurate with the dosage of the drug, peristalsis being inhibited somewhat longer than rhythmic segmentation.<sup>305</sup> Dibutoline sulfate, a new synthetic antispasmodic drug, proved to be effective in alleviating the pain accompanying the smooth muscle spasm in a few cases of ulcerative colitis, spastic colitis, pylorospasm and premenstrual cramps.<sup>306</sup> Dryness of the mouth was the only side reaction noted.

A series of roentgenograms taken after ingestion of 100 cc. of a feeding mixture with barium demonstrated that the material is transported aborally at a rate sufficient to permit its routine administration as early as twenty-four hours after operation.<sup>307</sup>

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304. Cantoni, G. L., and Eastman, G.: On the Response of the Intestine to Smooth Muscle Stimulants, *J. Pharmacol. & Exper. Therap.* **87**:392-399, 1946.

305. Wakim, K.; Powell, C. E., and Chen, K. K.: The Effects of B-Dimethylaminoethyl Benzilate Hydrochloride on Intestinal Activity, *Gastroenterology* **7**:213-217, 1946.

306. Cummins, G. M.; Marquardt, G. H., and Grossman, M. I.: Report of a Preliminary Clinical Trial of Dibutoline: A New Antispasmodic Drug, *Gastroenterology* **8**:205-207, 1947.

307. Rosenak, S., and Hollander, F.: Early Postoperative Motor Response of the Small Intestine to Jejunal Feedings, *S. Clin. North America* **27**:345-354, 1947.

Measured amounts of fatty acids mixed with a standard dog food (Pard) were fed to dogs.<sup>308</sup> Diarrhea resulted from the feeding of diets containing caprylic, caproic or butyric acids or the glycerides of each. Constipation followed feedings of stearic acid or tristearin.

Gregory<sup>309</sup> recorded intestinal tone and motility of Thiry-Vella loops of the upper jejunum in dogs with nausea and vomiting produced by the subcutaneous injection of doses of apomorphine varying from 0.02 to 0.10 mg. per kilogram of body weight. The first signs of nausea were accompanied with a rapid inhibition of intestinal tone and motility, followed by an equally rapid increase in tone maintained for several seconds before the development of retching; subsequently, the original tone and motility were regained. The response was abolished by denervation of the mesenteric pedicle to the loop. According to the author, these observations suggest that the response is of nervous origin and probably results from the excitation of central autonomic mechanisms.

*Absorption.*—Moseley and Chornock<sup>310</sup> studied the absorption of 10 per cent galactose from the upper intestine in 6 normal persons and in 5 with thyrotoxicosis and found that the thyrotoxic patient does not absorb galactose faster than the healthy person. Galactemia bears no constant relation to the amount of galactose absorbed, either in the normal or in the thyrotoxic patient. Galactemia may be decreased by the previous administration of dextrose without the rate of galactose absorption being disturbed. This observation supports the views of Folin, Berglund and Bodansky that availability of glucose is the deciding factor in the retention and utilization of galactose.

*Enzymes.*—Koehler and his associates,<sup>311</sup> studying the effect of cigaret smoking on the rate of flow and the concentration of the amylolytic, protolytic and lipolytic enzymes of the digestive secretions in man as obtained by transduodenal drainage, noted no significant changes.

*Gas.*—The average content of gas in the gastrointestinal tract of male subjects was estimated as approximately 1 liter, with variations throughout the day.<sup>312</sup> Defecation produced no appreciable reduction. The

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308. Wikoff, H. L.; Marks, B. H.; Caul, J. F., and Hoffman, W. F.: Some Effects of High Lipid Diets on Intestinal Elimination: IV. Saturated Fatty Acids, *Am. J. Digest. Dis.* **14**:58-62, 1947.

309. Gregory, R. A.: Changes in Intestinal Tone and Motility Associated with Nausea and Vomiting, *Am. J. Physiol.* **105**:58-65, 1946.

310. Moseley, V., and Chornock, F. W.: Intubation Studies of the Human Small Intestine: XXV. The Absorption of Galactose from the Intestine of Normal Individuals and Thyrotoxic Patients, *J. Clin. Investigation* **26**:11-17, 1947.

311. Koehler, A. E.; Hill, E., and Marsh N.: The Effect of Cigarette Smoking on Malnutrition and Digestion, *Gastroenterology* **8**:208-212, 1947.

312. Blair, H. A.; Dern, R. J., and Bates, P. L.: Measurement of Volume of Gas in the Digestive Tract, *Am. J. Physiol.* **149**:688-707, 1947.



amount of flatus passed by rectal tube in subjects on army K rations for a six day period varied from 12 to 340 cc. daily. With normal diets, the quantity of flatus averaged 200 cc. When soy bean was employed as the principal protein, amounts up to 2,600 cc. were passed daily. Large amounts of gas are passed when the motility of the intestine is high. Swallowed nitrogen may be almost completely absorbed if the motility of the intestine is low. The formation of gas from malted milk in the obstructed bowel of cats is significantly depressed by "sulfathaladine" and "sulfamethazine" (2-sulfanilamido-4, 6-dimethylpyrimidine).<sup>313</sup>

*Meckel's Diverticulum.*—In an excellent paper Kittle, Jenkins and Dragstedt<sup>314</sup> discuss the history, embryology, anatomy, pathologic processes, heterotopia, relation to other congenital anomalies and sex incidence of the diverticulum of Meckel. Two new cases of uncomplicated patent omphalomesenteric duct and 1 case in which prolapse occurred are presented. Four instances of peptic ulcer in Meckel's diverticulum are reported by Lund.<sup>315</sup>

In a series of 61 cases the highest incidence occurred during the second decade.<sup>316</sup> The main presenting symptom was abdominal pain. A preoperative diagnosis of appendicitis was made in 60 per cent; a correct clinical diagnosis was made in 12 per cent. Gastric mucosa was present in 24.6 per cent. Obstruction of the small bowel occurred in 5 of 22 cases reported by Haber.<sup>317</sup> Intestinal hemorrhage,<sup>318</sup> recurrent abdominal colic caused by torsion of the pedicle<sup>319</sup> and adenocarcinoma arising in a diverticulum<sup>320</sup> are reported.

*Congenital Stenosis.*—Two cases of congenital stenosis of the small intestine with retention of nonpenetrating foreign bodies are described.<sup>321</sup>

313. Segel, A.; Schweinburg, F. and Fine, J.: Effect of Sulfathaladine and Sulfamethazine on Gaseous Distention in the Obstructed Small Intestine of Cats, *Proc. Soc. Exper. Biol. & Med.* **63**:17-18, 1947.

314. Kittle, C. F.; Jenkins, H. P., and Dragstedt, L. R.: Patent Omphalomesenteric Duct and Its Relation to the Diverticulum of Meckel, *Arch. Surg.* **54**:10-36 (Jan.) 1947.

315. Lund, J.: Peptic Ulcer in Meckel's Diverticulum, *Bibliot. f. læger* **138**: 149-174, 1946.

316. Howell, L. M.: Meckel's Diverticulum: A Consideration of the Anomaly, with a Review of Sixty-One Cases, *Am. J. Dis. Child.* **7**:365-377 (April) 1946.

317. Haber, J. J.: Meckel's Diverticulum, *Am. J. Surg.* **73**:468-485, 1947.

318. Hanet, E.: L'hémorragies intestinales grave chez un enfane de douze ans: Ulcère du diverticule de Meckel, *Rev. méd. Liège* **2**:59-62, 1947. Girard, M.: L'hémorragie de l'ulcère, du diverticule de Meckel, *J. de méd. et chir. prat.* **117**:179-189, 1946.

319. Ingber, E.: Colicos abdominales por torsion decidivante del pedunculo de un diverticulo de Meckel degenerado, *Rev. méd. de Córdoba* **35**:530-591, 1946.

320. Costich, K. J., and McNamara, W. L.: Carcinoma of Meckel's Diverticulum, *Ann. Surg.* **124**:503-507, 1946.

321. Williams, M.: Congenital Stenosis of Small Intestine with Retention of Non-Penetrating Foreign Bodies: Report of Two Cases, *Ann. Surg.* **124**:492-496, 1946.

*Rupture.*—Kornblith<sup>322</sup> describes a case in which a 35 year old white man kicked in the abdomen eight hours previously but presenting no evidence of external trauma was found to have a rupture of the jejunum and generalized peritonitis due to *Bacillus welchi*, *B. coli* and the enterococcus. Closure of the perforation and chemotherapy resulted in recovery.

*Perforation.*—Twenty-two consecutive cases of perforation of the ileum were observed in a series of 1,077 cases of enteric fever; 11 of the patients were under observation when perforation occurred, and 11 were ambulatory<sup>323</sup> Perforation occurred early, usually within eleven days after the onset of illness. Pain was the predominant early symptom, usually generalized or near the umbilicus. Pelvic visceral irritation was manifested in 4 patients by dysuria and rectal tenesmus. Persistent diarrhea occurred only once. Perforation occurred at an average of 27.5 cm. from the ileocecal junction. Five deaths occurred among the ambulant patients and 7 in the nonambulant group, an over-all mortality of 55 per cent.

*High Altitude Bleeding.*—Severe intestinal hemorrhage occurred during exposure to low atmospheric pressure in the course of a simulated flight at high altitude.<sup>324</sup>

*Regional Enteritis.*—A corrugated steel clamp was applied momentarily to isolated segments of the small bowel of mongrel dogs.<sup>325</sup> The animals survived the initial injury without ill effects; slight loss in weight and occasional bloody stools were observed. When they were killed three to seven months later, the findings consisted of fibrous and omental adhesions, particularly on the antimesenteric side, round cell infiltration in the submucosa, lymphoid follicular hyperplasia and fibrous tissue proliferation.

Garlock<sup>326</sup> emphasizes the following five main types of symptoms in regional ileitis: (a) acute manifestations, usually erroneously diagnosed as indicative of acute appendicitis, (b) enteric symptoms, with the triad of foul, nonbloody diarrhea and cramps, weight loss and anemia (fever may be present, depending on the extent of the disease outside the bowel wall), (c) obstructive symptoms, (d) symptoms caused by involvement of adjacent viscera, such as vesical fistulas, and (e) the presence of external fecal fistulas. The lowest mortality and the best

322. Kornblith, B. A.: Rupture of the Jejunum Without Evident External Trauma, New York State J. Med. 46:1940-1941, 1946.

323. Dunkerley, G. E.: Perforation of the Ileum in Enteric Fever: Notes on Twenty-Two Consecutive Cases, Brit. M. J. 2:454-457, 1946.

324. Schier, W. W.: Massive Gastrointestinal Bleeding Following Exposure to Low Pressure, New England J. Med. 236:898-901, 1947.

325. Spellberg, M. A., and Ochsner, A.: The Role of Trauma as a Possible Etiologic Factor in Regional Enteritis: The Effect of Non-Penetrating Trauma on the Small Intestine of Dogs, Am. J. M. Sc. 213:579-584, 1947.

326. Garlock, J. H.: The Present Status of the Problem of Regional Ileitis, Am. J. Surg. 72:875-878, 1946.

late results are obtained when ileotransverse colostomy is performed, with exclusion of the ileum proximal to the upper limits of the diseased segment. After simple short-circuiting operations, complete recession of the nodal involvement has repeatedly been demonstrated at secondary laparotomy. Among nearly 100 patients so treated there have been no deaths, and follow-up studies have shown "the smallest percentage of recurrences." Homb<sup>327</sup> describes the pathologic appearance in the acute form of the disease.

Pratt and Ferguson<sup>328</sup> report 9 cases of what they choose to call "cicatrizing enterocolitis." The cause is thought to be some infection, most likely originating in the appendix, causing a "morbid" lymphadenitis in the mesenteric glands, with a subsequent or concurrent lymphedema. Appendectomy is recommended when laparotomy is performed in the early stages presumably for acute appendicitis. Crushing of the stump is to be avoided. Patients seen in the "ulcerative colitis stage" are treated medically for three months provided no significant stenosis has occurred. The disease subsides spontaneously in a high percentage of cases. The surgical procedure of choice for patients who are not improving is a by-passing operation, with exclusion and anastomosis of loops entirely free of the disease as shown by local examination and by the absence of enlarged mesenteric nodes. The mortality rate after resection, indicated in the obstructive stage, depends on the extent.

Extensive involvement of the ileum, cecum, ascending colon and transverse colon is described,<sup>329</sup> and other interesting cases are reported.<sup>330</sup> Intestinal obstruction and abscess secondary to regional ileitis were diagnosed in the seventh month of pregnancy in a case described by Babson.<sup>331</sup>

*Tuberculosis.*—In 6 instances of intestinal tuberculosis in patients with moderately extensive pulmonary disease, routine treatment, consisting of a low roughage diet, administration of vitamins A, C and D, and 5 cc. of 20 per cent calcium gluconate intravenously three times a week and the cautious use of ultraviolet rays, seemed to be helpful; proper treatment of the primary lesion in the lung was of the utmost importance.<sup>332</sup>

327. Homb, A.: On Acute Regional Enteritis, *Acts chir. Scandinav.* 4:343-357, 1946.

328. Pratt, G. H., and Ferguson, L. K.: Cicatrizing Enterocolitis, *Am. J. Surg.* 73:28-36, 1947.

329. Cash, I. I.; Pilcher, L. S.; Rappoport, A. E., and Barker, W. A.: Regional Ileitis Involving the Ileum, Cecum, Ascending Colon and Transverse Colon, *Ann. Int. Med.* 25:351-362, 1946.

330. Gogniaux, P.: Un cas d'ileite regionale, *Acta clin. belg.* 1:340-348, 1946. Fusaro, W. J.: Regional Ileitis, *Am. J. Surg.* 73:720-724, 1947.

331. Babson, W. W.: Terminal Ileitis with Obstruction and Abscess Complicating Pregnancy, *New England J. Med.* 235:544-547, 1946.

332. Keers, R. T.: Intestinal Tuberculosis: Some Observations, *Brit. J. Tuberc.* 41:3-37, 1947.

*Steatorrhea and Sprue.*—Steatorrhea is defined by Ricketts, Maimon and Knowlton<sup>333</sup> as an increase in the total amount of fecal fat above the normal of 10 to 20 Gm. per day or in the percentage of fat in the dry stool, the upper limit being about 20 per cent. The types of steatorrhea are listed as pancreatic, "idiopathic," including tropical and nontropical sprue and celiac disease, and miscellaneous, including obstruction of the mesenteric lymphatic vessels, intestinal lipodystrophy and lipogranuloma, gastrojejunocolic fistula, regional enteritis and sequelae of protozoan and bacillary dysenteries. Certain laboratory signs such as anemia, hypoproteinemia, hypocalcemia and impairment of fat absorption are common to most cases of steatorrhea, whatever the cause, and thus are of little help in the differential diagnosis. Likewise, determination of gastric acidity, serum amylase content, pancreatic enzymes in the intestinal contents, fecal nitrogen and the partition of fecal fat between neutral fat, fatty acids and soaps has been of no aid in distinguishing one type of steatorrhea from another. The first diagnostic step is a search for pathogenic organisms in the stools, since diarrhea on a parasitic or bacterial basis may result in excessive fat excretion. The next is a careful roentgenologic study of the gastrointestinal tract, including a roentgenogram of the abdomen designed to reveal calcification in the region of the pancreas. If the glucose tolerance curve is not flat and if there is no response to treatment with adequate amounts of crude liver extract (and folic acid), a condition other than "idiopathic" steatorrhea is likely, and if other studies have been unfruitful, surgical exploration may be indicated.

Shane and Deyke<sup>334</sup> believe that there are two etiologic factors in sprue; first, the deficiencies of "extrinsic" or "intrinsic" factors as proposed by Castle, Rhoads and Lawson; second, mechanical factors preventing absorption from the small bowel, such as lymphatic obstruction, and operative disturbances of anatomic relationships. Wingfield<sup>335</sup> concludes that the syndrome is due to a deficiency of some hypothetical substance contained in certain crude liver extracts. The course of sprue as observed in 680 cases<sup>336</sup> consisted in the appearance of diarrhea, anorexia and vomiting, usually in that order, followed by asthenia, loss of weight and dehydration. In the majority of cases (63 per cent) diet alone produced a remission. The symptoms of beginning remission were glossitis, cheilosis and angular stomatitis. Glossitis was present in 90

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333. Ricketts, H. T., Maimon, S. N., and Knowlton, K.: Steatorrhea, *M. Clin. North America* **31**:125-133, 1947.

334. Shane, S. J., and Deyke, V. F.: Observations on the Sprue Syndrome, *Canad. M. A. J.* **55**:448-450, 1946.

335. Wingfield, A. L.: Some Observations on the Etiology and Treatment of Sprue, *Proc. Roy. Soc. Med.* **39**:519-522, 1946.

336. Keele, K. D.: A Study of the Onset and Cyclic Development of the Sprue Syndrome, *Brit. M. J.* **2**:111-114, 1946.

per cent of the cases, usually during the transitional stage from relapse to remission or vice versa. Abdominal distention appeared, together with gain in weight, as the nausea, vomiting and diarrhea subsided. Scaling of the skin and loss of hair frequently accompanied the remission. Despite diets designed to contain 5 to 10 mg. of nicotinic acid and 3 mg. of riboflavin daily, an exacerbation of glossitis, which cleared in fourteen days without alteration in diet developed in 2 patients; in others the glossitis subsided without other treatment. Glossitis was minimal in the remissions induced with liver therapy. The degree of anemia was usually not severe in early cases, only 24 per cent of 600 patients having values for hemoglobin below 12 Gm. per cent. Macrocytic anemia was observed initially in 26 per cent of 80 cases. Macrocytosis without anemia was noted in 30 per cent, normal blood cell counts in 35 per cent and hypochromic anemia in 9 per cent. In remission, the change uniformly was from macrocytic anemia to macrocytosis only and then to normal blood counts. According to the author the return of the blood picture to normal always follows the return to normal weight

The development of the sprue syndrome in 3 servicemen who had returned from the Southwest Pacific theater is reported by Olson and Layne.<sup>337</sup> It is pointed out that sprue may develop in persons who have previously had diarrhea of bacillary or parasitic origin, with sufficient damage to the intestinal mucosa to impair absorption of essential food substances.

Diarrhea was the initial symptom in 1,069 patients with the sprue syndrome among Italian prisoners of war in India.<sup>338</sup> Ninety per cent presented signs of secondary deficiencies of the vitamin B type. Pigmentation of face, hands and abdomen, hypotension and mild hypochromic anemia were noted in the second week of the disease. A lowering of serum protein levels, edema and macrocytic hyperchromic anemia developed in untreated patients and in those in whom the diarrhea was not controlled within four or five weeks after the onset. Laboratory studies on 253 patients revealed low serum calcium levels, flat curves for the oral glucose tolerance test and urobilinogen in the urine. A 1,000 calorie, high protein, low fat diet was given during the acute phase of the disease, with an increase of protein for patients in whom severe anemia developed. Vitamins and liver extract were employed. Most patients recovered promptly. Twenty-three had relapses during every rainy season. In 4 cases the condition became chronic, and in 5 it terminated in aplastic anemia.

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337. Olson, S. W., and Layne, J. A.: Sprue as a Sequence to the War's Migration of Military Personnel, *Gastroenterology* 8:221-227, 1947.

338. Stefanini, M.: Observations on a Series of Cases of Sprue in a Prison Camp in India, *Gastroenterology* 8:729-734, 1947.

Black, Fourman and Trinder,<sup>339</sup> studying the feces in cases of sprue, noted that many patients seemed to respond well to sulfonamide compounds, which suggested the concomitant presence of bacillary infections or the prevalence of sulfonamide-sensitive organisms which though ordinarily not pathogenic assume pathogenic properties when there is an abnormal intestinal tract. The irritant character of the fatty stools seems to be due to soluble soaps and not to acidity. For detection in questionable cases, 100 Gm. of fat should be administered daily and stools examined over a four to ten day period, since the fat content varies. A high residue diet will lead to low values for the percentage of fat in dried stool. In the normal person the quantity of fat excreted daily should not exceed 10 Gm.

Bacteriologic and parasitic studies in 25 cases of tropical sprue<sup>340</sup> disclosed *Trichuris trichiura*, *Ascaris lumbricoides*, *Necator americanus* and a wide variety of organisms, the butyribacillus being found in 72 per cent. Though the blood picture and clinical manifestations improved with folic acid therapy, no significant change was noted in the parasitic and bacterial contents of the bowel as determined by proctoscopic swab.

Preliminary investigations of the mechanism of fat digestion were carried out on 10 patients with tropical sprue and on 8 normal subjects who served as controls.<sup>341</sup> With the use of a radiopaque double-lumened Miller-Abbott tube, intestinal contents were collected before and after ingestion of 25 cc. of olive oil. The secretions of controls appeared as uniformly suspended bile-stained emulsions; those of the patients with sprue contained whitish threads and clumps suspended in clear bile-stained fluid. Microscopically, all samples showed numerous fat droplets. In the samples from the controls these were evenly dispersed; in those from the patients with sprue they were aggregated in clumps. Stains indicated the presence of fatty acids and some well emulsified unsplit fat. It appears, therefore, that in the sprue syndrome fat is emulsified and, as would be expected from analysis of stool fat, hydrolyzed. The abnormality lies in either aggregation into clumps and threads of the fatty material or the failure to disperse such aggregations if they occur as a transitory phase of normal digestion. To assess the possibility of dispersing these clumps and threads, three specimens were incubated at 37 C. for four hours with fasting succus entericus which was (1) normal, (2) normal and mixed with ox bile, (3) obtained from patients with mild

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339. Black, D. A. K.; Fourman, P., and Trinder, P.: Faeces in Sprue, *Brit. M. J.* 2:418-420, 1946.

340. Milanes, F.; Curbelo, A.; Rodriguez, A.; Kouri, P., and Spies, T. D.: A Note on Bacteriological and Parasitic Studies of the Intestinal Contents of Patients with Sprue, *Gastroenterology* 7:306-313, 1946.

341. Smart, G. A., and Daley, R.: Fat Digestion in Sprue, Studied by Intestinal Intubation, *Lancet* 2:159-160, 1946.

sprue, (4) obtained from patients with mild sprue and mixed with ox bile, (5) obtained from patients with severe sprue and (6) obtained from patients with severe sprue and mixed with ox bile. Good dispersal of the clumps was observed in specimen 1, and moderate dispersal in specimen 3 and no dispersal in specimen 5. Addition of ox bile helped. In general, there is a rough correlation between the clinical severity of the disease and the degree of clumping. The investigations suggest that the clumps and threads consist mainly of fatty acids both finely dispersed and in droplet form bound in a mucin-like matrix. The problem remains whether the digestion of mucus is impeded in sprue because the mucus itself is abnormal or because the digestive juices lack mucus-splitting ferment.

Among 20 patients with sprue the lowest plasma tocopherol values occurred in persons who had suffered a relapse or who were experiencing early remission.<sup>342</sup> During relapse, a maximum rise in serum concentration of tocopherols of 0.09 mg. per hundred cubic centimeters was noted after an oral dose of 600 mg. of mixed tocopherols, in contrast to the mean maximal rise of 0.37 mg. in 7 healthy adults. In 17 patients experiencing a remission of sprue after a long period of treatment with liver extract the tocopherol levels were found to be essentially normal.

Between 5 and 10 per cent of patients with sprue acquired in military service have had low blood pressure, asthenia and signs of peripheral circulatory failure.<sup>343</sup> Ten of 41 patients had low values for serum sodium and serum chloride and, in some instances, a plasma volume which was low in relation to the body weight. The diminished serum sodium content was most pronounced. Studies of a typical patient revealed abnormal loss of sodium and a lesser degree of loss of chloride in the feces; in the urine chloride was lost and sodium was rapidly conserved. When the patient was on a high salt intake, sodium and chloride were retained, the blood pressure improved and signs of dehydration disappeared. The symptoms were attributed to salt deficiency modified by some degree of acidosis due to the preponderant loss of sodium over chloride. Serum potassium was not increased, and conservation of base by the kidneys was adequate. Loss of electrolyte in the copious watery stools probably accounts for the salt deficiency.

Harrison and others,<sup>344</sup> studying the potassium deficiency in a case of lymphosarcoma and the sprue syndrome, found an excessive fecal loss of potassium.

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342. Darby, W. J.; Cherrington, M. E., and Ruffin, J. M.: Plasma Tocopherol Levels in Sprue, *Proc. Soc. Exper. Biol. & Med.* 63:310-312, 1946.

343. Black, D. A. K.: Salt Deficiency in Sprue, *Lancet* 2:671-675, 1946.

344. Harrison, K. E.; Harrison, H. C.; Tompsett, R. R., and Barr, D. P.: Potassium Deficiency in a Case of Lymphosarcoma with the Sprue Syndrome, *Am J. Med.* 2:131-143, 1947.

An unusual case of nontropical sprue in a 15 year old boy is presented by Schein.<sup>345</sup> Death occurred from necrosis of the liver on the second day after his admission to the hospital. The clinical manifestations included diarrhea, bulky pale yellow stools containing a large amount of fatty acid crystals and neutral fat globules, fever, lymphadenopathy, acidosis, hypoprothrombinemia, hypocalcemia and tetany. Autopsy revealed an extensive and severe parenchymal degeneration of the liver, with fatty infiltration and dissociation of the hepatic cells, and an unidentifiable hyaline material disposed mainly as villous tip bands over the upper portions of the villi of the small intestine, whose characteristic deformation was "clubbing and mushrooming." In a second case also, that of a 71 year old man who presented a clinical picture suggestive of sprue, microscopic examination disclosed, though to a lesser extent, villous clubbing and hyaline villous tip bands.

Garcia Lopez and others<sup>346</sup> report rehabilitation of 18 patients with sprue treated with folic acid in daily doses of 25 to 200 mg. A daily oral dose of 10 mg. proved adequate in a series reported by Suarez and others,<sup>347</sup> small daily doses being more effective than fifty times as much given in a single dose. A daily dose of 20 mg. with an adequate diet produced better results than larger doses with an inadequate diet. An adequate maintenance dose seemed to be between 5 and 25 mg. per day.

Striking improvement in the roentgen appearance of the small bowel following the oral administration of 10 mg. of folic acid daily<sup>348</sup> was evidenced by a return to normal intestinal motility and by the establishment of a continuous column of barium not interrupted by segmentation or fragmentation; no change was detected in an untreated control patient.

A dramatic improvement occurred both in the blood picture and in intestinal absorption after synthetic folic acid was given to 2 previously untreated patients.<sup>349</sup> Two patients with sprue of long duration previously treated by administration of liver were improved subjectively, but little or no effect was observed on the blood.

Folic acid therapy failed to produce a significant rise in the red blood cell count or to restore the blood level and the hematologic picture to

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345. Schein, J.: Syndrome of Non Tropical Sprue with Hitherto Undescribed Lesions of the Intestine, *Gastroenterology* 8:438-460, 1947.

346. Garcia Lopez, G.; Spies, T. D.; Menendez, J. A., and Lopez Toca, R.: Folic Acid in the Rehabilitation of Persons with Sprue, *J. A. M. A.* 132:906-911 (Dec. 14) 1946.

347. Suarez, R. M.; Spies, T. D., and Suarez, R. M., Jr.: The Use of Folic Acid in Sprue, *Ann. Int. Med.* 26:543-677, 1947.

348. Hernandez Beguerie, R. L., and Spies, T. D.: Roentgenologic Studies on the Effect of Synthetic Folic Acid on the Gastrointestinal Tract of Patients with Tropical Sprue, *Am. J. Roentgenol.* 56:337-342, 1946.

349. Morrison, R. J. D., and Johnston, C. R.: Treatment of Tropical Sprue with Folic Acid, *Lancet* 1:636-637, 1947.



normal in 9 of 10 patients; in 7 adults the diarrhea was controlled and clinical improvement resulted, whereas no significant benefit was observed in 3 patients with celiac disease. Folic acid did not improve fat absorption as estimated by fat balance tests on 5 of 6 patients treated by Davidson and his associates;<sup>350</sup> on the other hand, Tegalaers and Weyers<sup>351</sup> noted improvement in fat absorption in 7 children treated by daily oral administration for thirty days of 10 mg. of folic acid.

*Intestinal Lipodystrophy.*—Pemberton and others<sup>352</sup> describe 3 additional cases of intestinal lipodystrophy (Whipple's disease); a fourth case is reported by Escudero and his associates.<sup>353</sup>

*Intussusception.*—Sixty-eight per cent of 95 infants and children with acute intussusception were under 1 year of age.<sup>354</sup> In 82.1 per cent no cause was found for the intussusception. A correct clinical preoperative diagnosis was made in 93 of the 95. The majority of intussusceptions occurred at the ileocecal junction. Resection resulted in a mortality rate of 42.8 per cent for 14 patients. The greatest single factor responsible for the high mortality rate was the prolonged duration of symptoms.

Subacute ileoileal intussusception occurring at a distance of over 3 feet (91 cm.) proximal to the ileocecal valve is reported by Tiscenco.<sup>355</sup> Operation confirmed the roentgenologic diagnosis. Intussusception occurred after intubation with a Miller-Abbott tube.<sup>356</sup> Retrograde intussusception of the large bowel into the small bowel, with chronic obstruction, was produced by a carcinoma of the cecum.<sup>357</sup> Finestone<sup>358</sup> reports an instance of intussusception of the excluded distal loop of ileum after ileocolostomy, with spontaneous expulsion per annum of the sequestered intussusceptum.

*Intestinal Obstruction.*—Harper and Lemmer<sup>359</sup> produced simple intestinal obstruction by inverting both ends of the divided small bowel in

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350. Davidson, L. S. P.; Girdwood, R. H., and Innes, E. M.: Folic Acid in the Treatment of the Sprue Syndrome, *Lancet* 1:511-515, 1947.

351. Tegalaers, W. H. H., and Weyers, H. A.: Influence of Folic Acid on Symptoms of Celiac Disease, *Maandschr. v. kindergeneesk.* 15:107-109, 1947.

352. Pemberton, J. deJ.; Comfort, M. W.; Fair, E. and Zaslow, J.: Intestinal Lipodystrophy (Whipple's Disease), *Surg., Gynec. & Obst.* 85:85-91, 1947.

353. Escudero, P.; Mosto, D., and Landabure, P. B.: Lipodistrofia intestinal de Whipple, *Rev. Asoc. méd. argent.* 60:795-803, 1946.

354. Oberhelman, H. A., and Condon, J. B.: Acute Intussusception in Infants and Children, *S. Clén. North America* 27:3-22, 1947.

355. Tiscenco, E.: Subacute Ileo-Ileal Intussusception in the Adult, *Brit. J. Radiol.* 19:374-380, 1946.

356. Nichols, H. M.: Intussusception Occurring After Intubation of Small Intestine, *Northwest Med.* 45:924-925, 1946.

357. Thorek, P., and Lorimer, W. S., Jr.: Retrograde Intussusception, *J. A. M. A.* 133:21-23 (Jan. 4) 1947.

358. Finestone, E. O.: Intussusception of Excluded Distal Ileum with Spontaneous Expulsion per Anum of Sequestered Intussusceptum, *Surgery* 21:34-42, 1947.

10 dogs at levels of 20 cm. below the pylorus, 100 cm. below the ligament of Treitz and 5 cm. proximal to the ileocecal valve. Water was given ad libitum. The average survival rate for animals with high obstruction was 9 days, for those with midileal obstruction 5.5 days and for dogs with low ileal obstruction 7.7 days, which indicates that, contrary to common belief, the higher the obstruction the greater the longevity. The main causes of symptoms and deaths appeared to be loss of fluid and electrolytes, distention, necrosis and ulceration of the intestinal wall, with possible absorption of toxins from bacteria, tissue necrosis and intestinal contents. The writers postulate that the reason human beings die of ulceration and perforation is that while fluid loss and electrolyte imbalance are easily corrected the relief of distention, which leads to necrosis and ulceration, is not so simple. Further observations showed that the normal intestinal bacteria acting on an ischemic distended bowel were responsible for ulceration and perforation and that the lower the obstruction the greater was the distention, necrosis and ulceration and the higher was the incidence of positive cultures of peritoneal and heart blood at autopsy.

In an interesting study by Blain and his associates<sup>360</sup> on the effect of penicillin, 10 dogs were subjected to artificial strangulation of the terminal 60 cm. of ileum by ligation of all vessels supplying this segment. Vomiting, distention, ascites and paralysis of the extremities developed in 5 animals serving as controls and given no treatment other than parenteral administration of fluids, and they died within twenty-six to thirty-six hours. The strangulated segments showed gross and microscopic evidence of ulceration, with intramural hemorrhage. The 5 animals treated with massive doses of penicillin were alive seventy-two hours later, after which time the strangulated bowel was resected; 1 died eight hours later and the other 4 recovered completely. Acute ulcerative enteritis was found in both the controls and the treated dogs. The authors conclude that the administration of massive doses of penicillin is a useful adjunct in the management of obstruction with strangulation but it does not supplant surgical intervention.

Obstruction of the small intestine due to adhesions and bands is discussed in a two hundred page monograph by Krook,<sup>361</sup> with particular reference to the causes of recurrence. The clinical features of obstruction of the small bowel are considered by Hunt.<sup>362</sup> Roentgen examina-

359. Harper, W. H., and Lemmer, R. A.: Necrosis and Ulceration of the Intestinal Wall in Simple Intestinal Obstruction: An Experimental Study, *Bull. Johns Hopkins Hosp.* **79**:207-228, 1946.

360. Blain, A. III; Kennedy, J. D.; Calihan, R. J., and Harkins, H. N.: Effect of Penicillin in Experimental Intestinal Obstruction, *Arch. Surg.* **53**:378-386 (Oct.) 1946.

361. Krook, S. S.: Obstruction of the Small Intestine Due to Adhesions and Bands, *Acta chir. Scandinav.*, 1947, supp. 125, pp. 1-200.

362. Hunt, C. J.: Early Indications of Adhesive Small Bowel Obstruction, *Am. J. Surg.* **72**:865-868, 1946.

tion of the abdomen should be done early in every case of abdominal distention in which there is a possibility of a mechanical obstruction of the bowel. Levitin<sup>363</sup> recommends that routine roentgenograms of the abdomen include a view of the organ in the lateral decubitus position in addition to the upright view. An instance is cited wherein a roentgenogram taken at the bedside with the patient lying on the left side disclosed free air in the abdomen (perforated peptic ulcer) whereas the upright view failed to do so. The lateral view is particularly useful also in the diagnosis and differentiation of paralytic and mechanical ileus. The tendency in both conditions for the gas to rise and the fluid to seek a common level because of free communication between the loops of distended bowel is best demonstrated in the lateral views. The increased prominence of the valvulae conniventes in mechanical obstruction is best shown by such views. They often reveal more effectively than the upright position the shadows cast by the properitoneal fat pad.

Hendricks and Griffin<sup>364</sup> report an analysis of 352 cases of obstruction; in 168 cases the obstruction was in the small bowel, and in 184 it was in the large bowel. Adhesions were the main cause of obstruction in the small bowel, the ileum being involved in 89.4 per cent. Resection was performed in 34 per cent, with a total mortality of 27.9 per cent. Carcinoma was the cause of obstruction in the colon in 90 per cent of the cases.

Eliason and Welty,<sup>365</sup> in a statistical survey of 292 cases, found that the mortality was not appreciably influenced by the completeness or suddenness of the obstruction. The mortality rate was 10 per cent in 176 cases of partial obstruction and 12 per cent in 116 cases of complete obstruction. Eleven per cent of the 153 patients with acute obstruction died, as did 11 per cent of 139 with chronic obstruction. The mortality rate was 8 per cent in 184 cases involving the small bowel and 16 per cent in 114 involving the large bowel. Carcinoma probably accounts for the high mortality in the latter group. The commonest causes of obstruction were adhesions (27 per cent), malignancy (20 per cent), hernia (23 per cent), lymphopathia venereum (14 per cent) and postoperative obstructions (11 per cent). The causes were miscellaneous in 5 per cent. In 59 cases malignant growths were accompanied with obstruction, with a mortality of 34 per cent. The mortality among 13 patients with femoral hernia was 31 per cent. The mortality for patients subjected to resection was 19 per cent as compared with 11 per cent for those not operated on. The causes of death were as follows: peritonitis

363. Levitin, J.: Scout Film of the Abdomen, *Radiology* **47**:10-29, 1946.

364. Hendricks, W., and Griffin, W. D.: Intestinal Obstruction, *S. Clin. North America* **27**:51-72, 1947.

365. Eliason, E. L., and Welty, R. F.: A Ten Year Survey of Intestinal Obstruction, *Ann. Surg.* **125**:57-65, 1947.

in 25 per cent of the cases, carcinoma in 22 per cent, pulmonary embolism in 16 per cent, pneumonia in 13 per cent and cardiovascular-renal disease in 9 per cent. In 15 per cent death was due to other causes. The mortality was reduced by one half after the introduction and use of the Miller-Abbott tube, decreasing from 18 to 9 per cent. Improvement in surgical technic and supportive and antibiotic therapy are thought to have played a role in the reduced mortality.

Devine<sup>366</sup> conceives paralytic ileus as characterized by three stages. In the first stage intestinal movements are active, coordinated and responsive to stimulation; in the second, movements are incoordinated, irregular and ineffective and in the third there is a complete disappearance of intestinal movement. Morphine is stressed as a useful prophylactic, since it increases the tone and frequency of small mixing waves even though peristalsis is decreased. Barbiturates decrease peristalsis and tone. During the stage of incoordinated and ineffective movements, stimulants such as enemas or pituitary extracts are likely to increase distention and pain rather than to relieve them. It is pointed out that true paralytic (idiopathic) ileus is rare and that localized peritonitis, abscess and pockets of infection are by far the more common causes. It is further stressed that drugs, intubation, enemas and stupes do not afford relief. In cases of fully developed paralytic ileus intubation, with fluid and electrolyte replacement, is the treatment of choice. Ileostomy or jejunostomy does not "cure" paralytic ileus.

Evans and Bigger<sup>367</sup> emphasize the importance of early diagnosis and surgical intervention in the treatment of obstruction from strangulation. The authors recommend laparotomy if the differentiation between simple and strangulating obstruction cannot be made within twenty-four hours after the onset since the lethal factors in strangulation, namely, shock and peritonitis, may soon become irreversible.

Schwartz<sup>368</sup> reports the sixth case of obstruction caused by a congenital adhesive band compressing the sigmoid in a 3 day old male infant. Obstruction in 2 cases was attributed to hematoma.<sup>369</sup> Severe intestinal obstruction occurred twelve hours after the ingestion of barium in a case of carcinoma of the hepatic flexure.<sup>370</sup> Intubation was successful

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366. Devine, J.: A Concept of Paralytic Ileus: A Clinical Study, *Brit. J. Surg.* **34**:158-179, 1946.

367. Evans, E. I., and Bigger, I. A.: Early Recognition and Management of Intestinal Strangulation, *J. A. M. A.* **133**:513-517 (Feb. 22) 1947.

368. Schwartz, A. R.: Mesenteric Bands Producing Intestinal Obstruction in a Three-Day-Old Infant with Recovery, *Arch. Pediat.* **63**:317-319, 1946.

369. Dealy, F. N., and Miceli, P. A.: Intraperitoneal Hemorrhage Complicating Simple Large Bowel Obstruction, *Surgery* **21**:542-545, 1947.

370. Stalker, L. K.: Barium as a Factor in Intestinal Obstruction, *Am. J. Surg.* **72**:756-757, 1946.

in 96 per cent of 200 cases of intestinal distention; a single-lumened tube with a mercury-weighted, balloon-tipped head was used.<sup>371</sup> Cecostomy and the passage of a Miller-Abbott tube through the cecostomy opening for the purpose of "back-flushing" and also for decompression of the anastomosis are recommended in the management of obstruction of the colon.<sup>372</sup>

*Necrosis.*—Jeckeln<sup>373</sup> describes a peculiar necrosis of the intestinal mucosa observed in thirty-five postmortem specimens and in seven surgical specimens. The fully developed process is characterized by necrosis of the mucosa, with a sloughing of the submucosa and the muscularis. Microscopic examination reveals thrombosis in the vessels of the submucosa. Hemorrhage and perforation may occur. The upper portion of the small intestine is usually the site of the severest involvement, although other portions of the small bowel and even the colon may be involved. Clinically, the onset is usually acute, with severe colicky pains in the upper part of the abdomen, usually most severe on the left.<sup>374</sup> Constipation is followed by bloody diarrhea. The sedimentation rate and the leukocyte count are increased. Early complications include peritonitis, paralytic ileus, diplegia or tetraplegia and Landry's paralysis as the result of capillary hemorrhages in the brain and in the spinal cord. The cause is still unknown, but dysentery, cholera or arsenical poisoning are said to have been excluded. The mortality averages about 40 per cent.

*Benign and Malignant Tumors.*—Sixty-five tumors of the small bowel, thirty-three of them malignant, reviewed by Botsford and Seibel<sup>375</sup> included eighteen adenocarcinomas, sixteen argentaffinomas, thirteen lymphosarcomas, nine lipomas, five adenomas, two leiomyomas and two fibromas. Forty-one were located in the ileum. Palpable masses were rare except in cases of lymphosarcoma, being present in 11 of 13 such cases. The diagnosis depends on thorough roentgenologic investigation of the small bowel in every patient with suggestive symptoms. Cattell and Colcock<sup>376</sup> report five tumors of the small intestine.

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371. Cantor, M. O.; Kennedy, C. S., and Reynolds, R. P.: Use and Abuse of Intestinal Decompression Tube: A Study Based upon Two Hundred Cases, *Am. J. Surg.* **73**:437-449, 1947.

372. Millet, J. B.: Cecostomy and the Miller-Abbot Tube: A Report on Their Combined Use in the Preparation of the Obstructed Large Bowel for Surgery, *Surg., Gynec. & Obst.* **84**:1083-1086, 1947.

373. Jeckeln, E.: Intestinal Necrosis: I. Pathologic and Anatomic Aspects, *Deutsche med. Wchnschr.* **72**:105, 1947.

374. Ruppert, C.: Intestinal Necrosis: II. Clinical Aspects, *Deutsche med. Wchnschr.* **72**:108, 1947.

375. Botsford, T. W., and Seibel, R. E.: Benign and Malignant Tumors of the Small Intestine, *New England J. Med.* **236**:683-694, 1947.

376. Catell, R. B., and Colcock, B. P.: Tumors of the Small Intestine, *S. Clin. North America* **27**:644-650, 1947.

The roentgen features of sarcoma of the small intestine, according to Root,<sup>377</sup> are involvement of a long segment, rigidity of the wall, lack of peristalsis, ulceration and a filling defect or stenosis.

Anemia was an outstanding feature in 2 patients with an adenocarcinoma of the jejunum and a benign leiomyoma of the ileum, respectively, in whom roentgen studies did not reveal the disease.<sup>378</sup> Massive hemorrhage occurred in a case of jejunal leiomyosarcoma.<sup>379</sup> The outstanding symptoms in carcinoma of the jejunum were those of chronic, progressive, intermittent obstruction.<sup>380</sup> A leiomyoma of the jejunum had been interpreted clinically as a duodenal ulcer.<sup>381</sup> Lymphoblastoma of the terminal end of the ileum was found in a soldier aged 30.<sup>382</sup> Two patients with malignant growths of the jejunum are alive and well six and one-half years after resection.<sup>383</sup> A melanosa of the ileum and brain appearing five years after removal of a primary tumor from the left leg is described.<sup>384</sup> Tumors of this type are rare, 25 cases in all having been reported in 1945. Of these, the disease was considered primary in 9. In the case reported there were no abdominal symptoms or signs to suggest the intestinal lesion.

A solitary, sclerosed, polypoid hemangioma produced intermittent intussusception and resulted in chronic partial intestinal obstruction.<sup>385</sup> The patient, a 50 year old woman, complained of intermittent, colicky, epigastric pain for five years, accompanied with melena and normocytic anemia. Dilatation of the proximal end of the jejunum was demonstrated in roentgenograms.

*Pneumatosis Intestinalis*.—Gaseous accumulations within the wall of the intestine, known as pneumatosis cystoides intestinalis, are primarily diagnosable by roentgen study.<sup>386</sup> Gas shadows lying within the contour of the bowel together with inconstant filling defects of increased trans-

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377. Root, J. C.: Neoplasms of the Small Intestine, *Cleveland Clin. Quart.* **14**:81-89, 1947.

378. Mourot, A. J., and Watkins, C. H.: Tumors of the Small Intestine, *Am. J. Surg.* **73**:385-389, 1947.

379. Collins, E. N., and Spencer, F.: Massive Hemorrhage Due to Leiomyosarcoma of the Jejunum, *Cleveland Clin. Quart.* **14**:1-6, 1947.

380. Sawyer, K. C.; Workman, C. W., and Queen, F. B.: Carcinoma of the Jejunum, *Rocky Mountain M. J.* **44**:287-289, 1947.

381. Marshall, S. F., and Welch, M. L.: Leiomyoma of the Jejunum, *New England J. Med.* **236**:95-97, 1947.

382. Galluccio, A. C.: Lymphoblastoma of the Terminal Ileum, *New York State J. Med.* **46**:2049-2052, 1946.

383. Connolly, E. A., and Lempka, A. W.: Jejunal Malignancy, *Surgery* **21**: 901-910, 1947.

384. Spier, J., and Wood, E. C.: Metastatic Melanocarcinoma Involving the Small Intestine and Brain, *New England J. Med.* **263**:824-828, 1947.

385. Browne, D. C., and McHardy, G.: Solitary Sclerosing Hemangioma of the Jejunum, *Gastroenterology* **8**:665-667, 1947.

386. Lerner, H. H., and Gazin, A. I.: Pneumatosis Intestinalis: Its Roentgenologic Diagnosis, *Am. J. Roentgenol.* **56**:464-469, 1946.

lucency are pathognomonic. Crepitation may be noted in a distended loop of bowel on physical examination.

#### PARASITIC AND DIARRHEAL DISEASES

*Enteric Infections.*—Kirsner<sup>387</sup> reemphasizes the need for a constant awareness of the possible presence of bacillary dysentery, amebic dysentery and food poisoning among outbreaks of acute diarrhea. The clinical features of these diseases are reviewed, and present methods of diagnosis and therapy are described. Baird<sup>388</sup> discusses the causes of chronic diarrhea.

Nineteen outbreaks of epidemic diarrhea of the newborn were reported to the Massachusetts Department of Public Health from 1935 to 1945, with morbidity rates of 49 and 21 per cent for premature and full term infants respectively and mortality rates of 53 and 25 per cent.<sup>389</sup> Investigation revealed many inadequacies in the operation of the nurseries.

A virus or viruses rendering the intestinal mucosa vulnerable to secondary bacterial invasion is suggested by studies of acute enteritis in the Middle East.<sup>390</sup> Kershaw<sup>391</sup> regards as fallacious the tendency to attribute all nonspecific diarrheas to infection and supports the view that many are caused by sudden chilling of the abdomen.

A fatal case of acute enterocolitis resulting from administration of a markedly hypertonic alkaline enema to a 6 year old child is reported.<sup>392</sup> Because of mild abdominal distention and restlessness, the child was given an enema consisting of a half cup of soda (about 130 Gm.), a half cup of sugar and a half cup of salt in a quart (946 cc.) of tepid water. Within a minute after slow administration had been completed, abdominal pain, cramps and vomiting ensued, followed by coma. Nine hours later, generalized convulsions were followed by death. Autopsy revealed extensive epithelial necrosis, ulceration, congestion and leukocytic infiltration in the large bowel and to a lesser degree in the small intestine. The submucosa of the stomach was congested and edematous. An outstanding finding was the presence of early necrosis of the germinal centers of the lymphoid follicles both in Peyer's patches and in the spleen.

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387. Kirsner, J. B.: Acute Enteric Infections, *M. Clin. North America* **31**:113-124, 1947.

388. Baird, M.: Chronic or Recurrent Diarrhea, *Canad. M. A. J.* **55**:273-278, 1946.

389. Rubenstein, A. D.: Epidemic Diarrhea of the Newborn in Massachusetts, *New England J. Med.* **236**:87-94, 1947.

390. MacGregor, I.: Acute Enteritis in Subtropical Climates, *Brit. M. J.* **2**:225, 1946.

391. Kershaw, G. R.: Acute Non-Specific Diarrhea and Dysentery, *Brit. M. J.* **2**:717-719, 1947.

392. Lindsay, S.: Acute Enterocolitis and Death Resulting from a Markedly Hypertonic Enema, *Gastroenterology* **7**:364-370, 1946.

The clinical course and almost identical pathologic lesions were reproduced in guinea pigs by enemas of the same composition.

*Food Poisoning.*—In an epidemic of food poisoning, seven enterotoxic strains of staphylococci were isolated from the throat and feces of patients, from vegetable salad and from cooked ham.<sup>393</sup> Because these organisms were lysed by two lysogenic types of staphylococci and also produced a phage which lysed two cultures of staphylococci, it was concluded that they were identical and that the organism isolated from the food caused the outbreak.

*Salmonella Infections.*—An efficient and rapid method for the isolation and identification of enteric pathogenic organisms is reported.<sup>394</sup> In a study of 86 sporadic instances of salmonellosis during the period 1941 to 1945, twenty-one serologically identified strains were encountered.<sup>395</sup> *Salmonella choleraesuis*, *Salmonella typhimurium*, and *Salmonella Oranienberg* were recovered in 11, 20 and 16 cases respectively. There was a wide variation in the type of clinical syndromes, which ranged from simple diarrhea to septicemia, and in their severity. Thirteen patients died; 9 were subjected to autopsy. The typhoid-like lesions caused by *S. typhimurium* are emphasized. *Salmonella choleraesuis* seemed to produce the clinical picture of sepsis with the greatest regularity. *Salmonella Oranienberg* produced a relatively mild picture of enteritis, while the condition caused by *S. typhimurium* tended to be of moderate severity, although there were some fatalities.

An outbreak of gastroenteritis among the pupils of a high school in Habana, Cuba, was caused by *S. typhimurium*.<sup>396</sup> The source was traced to the water tank, in which a dead rat was found. The outbreaks ceased when the suspected water supply was shut off.

Five cases of *Salmonella* fever, in all of which the blood culture yielded the organism, were seen in an overseas hospital on Luzon, Philippine Islands.<sup>397</sup> The clinical manifestations varied from a severe systemic infection with pulmonary involvement, cholecystitis and subsequent perforation of the gallbladder to a moderate febrile course with only malaise and headaches. Offending organisms were *Salmonella paratyphi A* in 3 cases, *S. enteritidis* in 1, and a member of group C *Salmonella* in 1.

393. McClure, W. B., and Miller, A. M.: Identification of Identical Strains of Staphylococci in Food Poisoning and Other Infections by Bacteriophage Typing, *Canad. M. A. J.* 55:36-39, 1946.

394. Fullgarbe, E. A., and Levant, F. A.: Isolation and Identification of Enteric Pathogens at a Naval Base in North Africa, *U. S. Nav. M. Bull.* 46:1398-1402, 1946.

395. Angrist, A., and Mollov, M.: Bacteriologic, Clinical and Pathologic Experience with Eighty-Six Sporadic Cases of *Salmonella* Infection, *Am. J. M. Sc.* 212:336-346, 1946.

396. Reaud, A.: An Outbreak of Gastro-Enteritis Caused by *Salmonella Typhimurium*, Presumably Water-Borne, *South. M. J.* 40:176-180, 1947.

397. Bender, C. E.: *Salmonella* Fever, *Northwest Med.* 45:660-665, 1946.



A case is described <sup>398</sup> in which the etiologic agent was found to be a paracolon organism closely related antigenically to the Q-1030 strain of nonmannitol fermenting dysentery bacilli described in 1943 by Sachs; it was resistant to the sulfonamide drugs but sensitive to streptomycin.

In an infection due to *Bacillus paratyphosus* B (*Salmonella schottmülleri*), no benefit was obtained with streptomycin therapy; the organism was demonstrated to be markedly resistant to streptomycin in vitro.<sup>399</sup> In *Salmonella suispestifer* bacteremia, streptomycin apparently had no effect on the course of the illness, although the organism was somewhat susceptible in vitro.

*Bacillary Dysentery.*—Experimental bacillary dysentery can be successfully produced in man by ingestion of approximately one billion *Shigella* organisms in water.<sup>400</sup> A strain of *Shigella*, extremely virulent for mice, failed to produce clinical infection in man, while other strains of much lower virulence for mice produced moderate or severe dysentery in man. The incubation period in the experimental disease varied from twenty-four to seventy-two hours. Sulfadiazine effectively controlled the dysentery produced by sulfadiazine-susceptible strains of *Shigella* organisms, and it rapidly suppressed the carrier state.

An epidemic of Sonne dysentery occurred in a large general hospital<sup>401</sup> intermingled with infections for which the cause, after careful investigation, could not be determined but which were similar clinically to those caused by *Bacterium sonnei*.

Sulfacarboxythiazole (2-sulfanilamido-5-carboxythiazole) was found to be poorly absorbed when given orally, with blood concentrations usually below 1 mg. per one hundred cubic centimeters.<sup>402</sup> The amount of excretion of the drug in the stools varied between 83 and 92 per cent of the amount ingested and that in the urine between 3 and 7 per cent. Satisfactory clinical results were obtained for 44 of 50 patients with diarrhea caused chiefly by dysentery organisms. Toxic reactions developed in 6 cases, including persistent diarrhea in 4, nausea and vomiting in 1 and a nodular cutaneous rash in 1 patient.

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398. Luippold, G. F.: A Paracolon Organism Antigenically Related to the Sachs Q-1030 Bacillus and Associated with Chronic Enterocolitis, *Gastroenterology* 8:358-366, 1947.

399. Morgan, H. J., and Hunt, J. S.: Streptomycin in Clinical Practice: A Review and Case Reports, *Am. Pract.* 1:73-86, 1947.

400. Shaughnessy, H. J.; Olsson, R.; Bass, K.; Friewer, F. and Levinson, S. O.: Bacillary Dysentery in Human Volunteers, *Yale J. Biol. & Med.* 19:537-546, 1947.

401. Martin, L., and Wilson, M. M.: Sonne Dysentery and Non-Specific Gastroenteritis in a Hospital, *Lancet* 1:553-55, 1947.

402. Hirsh, H. L.; Hickman, T. L.; Sweet, L., and Dowling, H. F.: Sulfacarboxythiazole: Absorption, Excretion, Toxicity, and Therapeutic Results in Bacillary Dysentery and Non-Specific Diarrhea, *J. Lab. & Clin. Med.* 31:1305-1313, 1946.

In an epidemic among army personnel on board ship, and subsequently after they landed, *Shigella paradysenteriae* (Flexner) was recovered repeatedly from the stools.<sup>403</sup> Suggestive evidence is presented to support the view that flies, particularly the "blue bottle" variety, were instrumental in propagating the disease. Treatment consisted of sulfadiazine and supportive therapy along with hospitalization when possible. Morphine was used liberally to control pain and diarrhea. The results in general were extremely good. During this epidemic, and in others among Australian troops, superficial proctitis was observed during the height of the disease and in the convalescent period, but chronic ulcerative colitis did not develop.

*Typhoid.*—The symptoms in 360 cases of typhoid fever are analyzed.<sup>404</sup> Anorexia was present in 90 per cent, abdominal tenderness in 84 per cent, abdominal distention in 76 per cent, foul breath and sordes in 69 per cent, nausea and vomiting in 54 per cent, intestinal hemorrhage, rarely severe, in 21 per cent, diarrhea at some time in the course of the disease in 43 per cent and constipation in 79 per cent. There were 7 proved instances of perforation (5 ileal and 2 appendical) and 4 instances of probable perforation; meteorism seemed to precede perforation.

*Trichinosis.*—An outbreak of trichinosis resulting chiefly from the ingestion of uncooked sausage is reported by Shookhoff and his associates;<sup>405</sup> there were no fatalities. Gastrointestinal symptoms occurred in a minority of the cases; the onset of such symptoms was usually simultaneous with the appearance of edema. The commonest initial manifestations were edema of the eyelids and fever. The classic prodromal gastroenteritis occurred in only 7 cases. Eosinophilia was the most constant early laboratory finding. The precipitin test was found more useful than the intradermal test as the reaction to it became positive earlier.

*Intestinal Parasites.*—Of 59 soldiers in New Guinea studied because of eosinophil counts of 9 per cent or more, 47 (79 per cent) were found to have intestinal helminthic infections. Forty-two (71 per cent) had hookworm disease and 5 (8 per cent) had strongyloidiasis. The high count in 12 (20 per cent) was unexplained.<sup>406</sup> The diagnosis of *Strongyloides* infection in 4 of 5 cases was made by examination of duodenal fluid; larvae were not found in the feces.

Among 1,114 patients from the South Pacific area, *Endamoeba coli* was found in 4.9 per cent and *Endolimax nana* in 19.4 per cent.<sup>407</sup> Of

403. Brown, P. W.: Bacillary Dysentery, *Gastroenterology* 7:525-527, 1946.

404. Stuart, B. M., and Pullen, R. L.: Typhoid: Clinical Analysis of Three Hundred and Sixty Cases, *Arch. Int. Med.* 78:629-661 (Dec.) 1946.

405. Shookhoff, H. B.; Birnkrant, W. B., and Greenberg, M.: An Outbreak of Trichinosis in New York City, *Am. J. Pub. Health* 36:1403-1411, 1946.

406. Denhoff, E.: The Significance of Eosinophilia in Abdominal Complaints of American Soldiers, *New England J. Med.* 236:201-206, 1947.

407. Zarrow, M., and Rifkin, H.: Intestinal Parasites Diagnosed at an Army General Hospital, *Am. J. M. Sc.* 212:289-293, 1946.

3,415 soldier patients examined for helminth infestation, 13.2 per cent were found to have hookworm. During 1943, the stools of 375 of 1,371 patients (27 per cent) examined for parasites at a Naval Hospital in New Zealand contained parasites, hookworm and *Endamoeba histolytica* being present in 116 and 97 cases respectively. Eight other pathogens were found in small percentages of the group.<sup>408</sup> Strongyloidiasis responded well to gentian violet medicinal, intraduodenal instillation of a 1 per cent solution being employed in the resistant cases. Hamilton<sup>409</sup> reports the roentgenologic diagnosis of infestation with *Taenia saginata*; the evacuation roentgenogram clearly showed a long, ribbon-like defect in the ileum.

*Amebiasis*.—Roberts<sup>410</sup> in an important study has shown that flies, given access to infected material, may transmit *E. histolytica* cysts in their feces for periods extending from five minutes to at least thirty-one hours.

Miller<sup>411</sup> believes that the over-all incidence of *E. histolytica* in Canada is approximately 2 per cent but that it may be higher in special groups. An incidence of 13 per cent is reported among 500 servicemen returning from the subtropics; the incidence in three institutions was 20, 23 and 37 per cent respectively.

It is not definitely known whether the drugs commonly used in the treatment of amebiasis exert their influence primarily by inhibition or by destruction of the organisms. Since there is evidence that some degree of resistance to infection occurs, the standard antiamebic drugs and numerous other compounds were tested to determine their amebostatic properties.<sup>412</sup> It was found the paraaminobenzoic acid (PABA) equaled emetine and vioform in this respect; hence, paraaminobenzoic acid and two other compounds (2-n-heptyl-4, 6, diamino-s-triazine and 2-methyl-4-amino-5-bromomethyl-pyrimidine) deserve a trial if their pharmacologic and toxicologic properties permit. Most antimalarial drugs were found inactive. Vioform and emetine were inhibitory at concentrations of about 0.5 mg. per hundred cubic centimeters (1:200,000). Paraaminobenzoic acid in the same concentration also was inhibitory. As in

408. Willard, J. H.: Intestinal Parasites in Service Personnel in the South Pacific, with Special Reference to the Incidence and Treatment of Strongyloidiasis, *Gastroenterology* 7:650-655, 1946.

409. Hamilton, J. B.: *Taenia Saginata*: A Case Report, *Radiology* 47:64-65, 1947.

410. Roberts, E. W.: Part Played by Feces and Vomit-Drop in Transmission of *Endameba Histolytica* by *Massa Domestica*, *Ann. Trop. Med.* 41:129-132, 1947.

411. Miller, M. J.: Is Amoebiasis a Medical Problem in Canada? *Canada. M. A. J.* 55:336-344, 1946.

412. Brackett, S., and Bliznick, A.: The Rate of Multiplication of *Endamoeba Histolytica* and Its Relation to in Vitro Drug Testing and Possibly to Nutritional Studies, *J. Parasitol.* 33:154-165, 1947.

in vitro studies, there is never complete assurance of similar results in vivo; chiniofon, for example, is only mildly active in vitro but effective clinically.

The clinical features of amebiasis and its complications are reviewed by various authors.<sup>413</sup> Lewis<sup>413b</sup> found the reaction to the complement fixation test to be positive in only 7 of 20 cases; in 6 of these the condition was severe. The reaction to the test in 20 carriers was negative. Complications developing in 57 per cent of the overseas patients included ulcerative colitis in 4, granuloma in 3, chronic diarrhea in 3, steatorrhea in 2, amebic abscess in 2, appendicitis in 2 and mucous colitis in 1. Of 5 patients for whom a previous diagnosis of "ulcerative colitis" had been made without the criteria being given, 1 had a history of both amebic and bacillary dysentery, 3 a history of amebic dysentery and 1 a history of undiagnosed dysentery acquired during an epidemic. All were treated with sulfadiazine and 3 with vioform; 4 "recovered," and 1 was transferred elsewhere. The total excretion of fat in twenty-four hours was measured in 26 cases. Normal persons excreted 1.0 to 5.0 Gm. and patients with mild diarrhea 3 to 9 Gm. Nine patients excreted 12 to 80 Gm.; of these, 1 had ulcerative colitis, 1 pancreatogenous steatorrhea and 7 a syndrome closely resembling tropical sprue. All in the latter group had served in New Guinea or in the Philippines for from one to three years. All gave a history of dysentery; amebic infection was proved in 2. The serum protein levels were normal or slightly reduced. The blood calcium or phosphorus levels were below normal in a few cases. The curve for the oral glucose tolerance test tended to be low and flat. The patients responded well to a diet of 40 Gm. of fat, 400 Gm. of carbohydrates and 120 Gm. of protein. Crude liver extract, 5 cc. twice weekly, was given.

Fletcher, Dougan and Sammon<sup>413c</sup> suggest that patients with an enlarged tender liver and with stools not containing amebas be treated with four injections of emetine hydrochloride to exclude the possibility of an hepatic abscess. A marked decrease in the size and tenderness of the liver occurs with the fourth injection.

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413. (a) Murray-Lyon, R. M.: The Aetiology and Diagnosis of Amoebiasis, *Edinburgh M. J.* **54**:65-75, 1947. (b) Lewis, R. A.: Enteric Infections and Their Sequelae, *New England J. Med.* **235**:571-581, 1946. (c) Kenamore, B.: Chronic Diarrhea in Military Personnel Returning from the Tropics, *Gastroenterology* **7**:528-532, 1946. (d) Morton, T. C.: Diagnosis of Chronic Dysentery in Service Personnel, *Brit. M. J.* **2**:890-893, 1946. (e) Fletcher, J. P.; Dougan, A. A., and Sammon, Q. M.: Amoebiasis, *Canad. M. A. J.* **55**:278-283, 1946. (f) Hayward, G. W.: Amoebiasis in Italy, *Brit. M. J.* **13**:457-459, 1946. (g) Klatskin, G.: Observations on Amebiasis in American Troops Stationed in India, *Ann. Int. Med.* **25**:773-788, 1946. (h) Cameron, J. D. S.: Amoebiasis, *Edinburgh M. J.* **54**:76-89, 1947. (i) Elsom, K. A.; Roger, A. M., and Wood, F. C.: Amebiasis: Observations in an Army General Hospital in India, *Gastroenterology* **8**:135-153, 1947.

Klatskin<sup>413g</sup> found that the routine administration of moderate doses (6 grains [0.36 Gm.] in six days) of emetine hydrochloride together with the intensive use of chiniofon and carbarsone retention enemas yielded a relapse rate of 5.6 per cent in 162 consecutive cases; in contrast a rate of 9.6 per cent was observed in 355 consecutive cases in which carbarsone and an iodine preparation were given if the patients were asymptomatic and an additional 4 grains (0.25 Gm.) of emetine hydrochloride in four days if they were symptomatic. Among more than 500 patients treated with emetine hydrochloride only one serious complication, severe myocarditis, occurred; the routine therapy erroneously was not carried out in this instance.

In a series of patients treated by Cameron<sup>413h</sup> in the early days of the war when emetine hydrochloride was the only amebicidal drug available, "cures" were obtained in about one third and temporary remission with subsequent relapse in one third and no effect was noted in the rest. Emetine hydrochloride was found to be ineffective in many conditions of the intestinal type, attributable presumably to the fact that the amebas in avascular necrotic and fibrous tissue were less accessible. A drop in blood pressure was the most common initial sign of toxicity to emetine hydrochloride, followed by an irregular pulse, heart block and myocardial changes. Neuritis with pain, weakness and paralysis were the chief nervous manifestations. No single amebicidal drug was found to be entirely effective. Combinations of emetine hydrochloride, diodoquin, carbarsone and succinylcufathiazole yielded the best results. Penicillin was given in secondary or concomitant bacterial infections. Hepatic abscesses rarely required surgical drainage. "Medical" aspiration was necessary when the abscess was large and fluctuant; others receded and disappeared with proper systemic treatment. Introduction of emetine hydrochloride into abscess cavities served no useful purpose.

Elsom and his associates<sup>413i</sup> report that the response to emetine hydrochloride was definite, prompt and sometimes dramatic. Four patients with amebic abscess, not responding to medical therapy, were treated with aspiration under direct observation at laparotomy.

Albright and Craig,<sup>414</sup> warning that the sources of amebic infection will increase with the return of troops from endemic areas overseas, emphasize also that the term "carrier state" is misleading, for the presence of the parasite in any form means invasion of the tissue. All asymptomatic "carriers" should be treated with emetine hydrochloride and an enteric drug such as chiniofon or carbarsone.

Amebiasis involving the cecum may simulate all types of cecal and appendical lesions, according to Wilbur and Camp.<sup>415</sup> The high mortality

414. Albright, E. C., and Gordon, E. S.: Present Status of the Problem of Amebiasis, *Arch. Int. Med.* 79:253-271 (March) 1947.

415. Wilbur, D. L., and Camp, J. D.: Amebic Disease of the Cecum: Clinical and Radiological Aspects, *Gastroenterology* 7:535-548, 1946.

from surgical therapy makes it imperative to distinguish amebiasis of the cecum from appendicitis. Smyth<sup>416</sup> calls attention to similarities between carcinoma and ameboma.

Various writers<sup>417</sup> emphasize further the importance of combining emetine hydrochloride and other drugs such as carbarsone, chiniofon and vioform in the therapy of amebiasis.

Dack and Moloshok<sup>417e</sup> describe toxic cardiac manifestations after emetine hydrochloride was given in total dosages ranging from 7 to 22 grains (0.45 to 1.32 Gm.). In some cases electrocardiographic abnormalities did not appear until one to two weeks after treatment had ended, and they persisted in some for two months or more. In a study of the role of secondary bacterial pathogens in amebic colitis, Ellenberg<sup>418</sup> treated 59 patients with 27 Gm. each of sulfadiazine over a five day period, with the result that in 98 per cent the condition either cleared or improved considerably; necrotic sloughs and diffuse inflammatory mucosal reactions, as viewed proctoscopically, disappeared, leaving clean-based ulcers. Siguier<sup>419</sup> reports that the simultaneous administration of penicillin, sulfonamide drugs and emetine hydrochloride to 100 patients resulted in permanent eradication of the amebas in 50 per cent; relapses occurred in the other 50 per cent at much longer intervals than those observed after the administration of emetine hydrochloride alone.

Bingham<sup>420</sup> discusses the surgical management of various complications of amebiasis such as pericolic infections, appendical involvement, and amebic abscess of the liver.

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416. Smyth, M. J.: Confusion of Amoeboma with Carcinoma, *Lancet* **2**:376-377, 1946.

417. (a) Murgatroyd, F.; Hargreaves, W. H.; Lovibond, J. L.; Somervell, T. H.; Morgan, C. N.; Wright, A. D., and Hunt, A. H.: Use of Medicaments in Disease of the Colon and Rectum, *Proc. Roy. Soc. Med.* **39**:541-550, 1946. (b) Karl, M. M., and Sloan, F. R.: The Management of Amebiasis, *Ann. Int. Med.* **25**:789-798, 1946. (c) Arnett, J. H.: Treatment of Carriers of *Endamoeba Histolytica* and Other Protozoa with Carbarsone, Chiniofon and Vioform, *Am. J. M. Sc.* **213**:608-610, 1947. (d) Monat, H. A., and Hertner, J. E.: Intractable Amebiasis, a Warning, with Report of a Case, *Mil. Surgeon* **99**:310-312, 1946. (e) Dack, S., and Moloshok, R. E.: Cardiac Manifestations of Toxic Action of Emetine Hydrochloride in Amebic Dysentery, *Arch. Int. Med.* **79**:228-238 (Feb.) 1947. (f) Rail, G. A.: Comparative Effect of Drugs Used in Treatment of Amebiasis, *J. Trop. Med.* **50**:3-12, 1947.

418. Ellenberg, M.: Amebiasis: The Role of Bacteria in Symptomatology: I. Sigmoidoscopic Findings in Symptomatic and Asymptomatic Cases; II. The Effect of Sulfadiazine on Symptoms and Sigmoidoscopic Findings, *Am. J. Digest. Dis.* **13**:356-360, 1946.

419. Siguier, F.: La methode d'Hargraves blanc dans le traitement des amibiases chroniques et à rechutes en milieu tropical d'après 100 observations, *Arch. d. mal. de l'app. digestif* **36**:33-62, 1947.

420. Bingham, D. L. C.: The Treatment of Some Surgical Complications of Amebiasis, *Canad. M. A. J.* **55**:341-344, 1946.

*Schistosomiasis*.—Faust,<sup>421</sup> testing the effect of cold on eggs of *Schistosoma japonicum*, found that a considerable proportion of eggs would survive and hatch under conditions approximating the cold season of South China; a smaller percentage would survive the winter in Central China and extremely few would remain viable in endemic areas in Japan. Alves and Blair<sup>422</sup> describe the preparation and use of a cercarial antigen for intradermal testing of the skin which gives a higher proportion of positive reactions than are revealed by repeated microscopic examinations. The cutaneous test is helpful also in assessing the efficacy of therapy. However, Faust<sup>423</sup> considers the demonstration of the eggs to be the only known method of specific diagnosis; skilled, experienced technicians and repeated examinations are required. In the late chronic stage, eggs are frequently fewer in number, immature and degenerate; in this stage the intradermal antigen reaction should be positive.

Among 495 soldiers who had been hospitalized overseas and treated with at least one course of "fuadin" (sodium antimony III bisulfate) or tartar emetic or both five to nine months previously, 156 were still passing eggs.<sup>424</sup> In the early part of the study, the direct smear method accounted for 88 per cent of the positive reactions and the gravity sedimentation technic for 38 per cent; 12 per cent were detected by the latter technic only. The direct smear, in combination with one or more procedures for sterilizing sedimentation, detects more infected stools than any one method alone.

Martin and others<sup>425</sup> found no constant or significant changes in the blood sedimentation rate or in the plasma protein level; eosinophilia was of slight significance. Competent examination of at least three successive stools is necessary.

Among 481 patients studied by Mason and others,<sup>426</sup> recurrent epigastric cramps and tenderness were the most frequent complaints on admission to the hospital. There was little evidence of hepatomegaly and

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421. Faust, E. C.: The Effects of Cold Temperature on the Eggs of *Schistosoma Japonicum*, *J. Parasitol.* **33**:134-137, 1947.

422. Alves, W., and Blair, D.: Diagnosis of *Schistosomiasis*: Intradermal Test Using a Cercarial Antigen, *Lancet* **2**:56-560, 1946.

423. Faust, E. C.: *Schistosomiasis Japonica*: Its Clinical Development and Recognition, *Ann. Int. Med.* **25**:585-600, 1946.

424. Hesselbrock, W. B.; Lippincott, S. W.; Palmer, E. D.; Henderson, E. W., and Pauls, F. P.: A Study of Various Methods of Stool Examination in the Diagnosis of *Schistosomiasis Japonica*, *Am. J. Clin. Path.* **17**:197-204, 1947.

425. Martin, W. B.; Graziani, J. G.; Collins, J., and Lincicum, D. R.: Chronic Infestation with Intestinal Parasites in an Engineer Battalion with Particular Reference to *Schistosoma Japonicum*, *South. M. J.* **39**:885-888, 1946.

426. Mason, P. K.; Daniels, W. B.; Paddock, F. K., and Gordon, H. H.: *Schistosomiasis Japonica*: Diagnosis and Treatment in American Soldiers, *New England J. Med.* **235**:179-182, 1946.

splenomegaly, although these were reputed to be the most frequent complications in the native population where the infestation was acquired. Repeated examination of the stools by more than one method was necessary to demonstrate the ova. Persistent eosinophilia was suggestive of the disease. In similar studies<sup>427</sup> a known relapse rate of 42 per cent was observed. Proctoscopic signs consisted of 1 to 2 mm. yellowish nodules, isolated or in clusters, with or without induration or superficial ulceration. Ova may be recovered in these nodules.

Cerebral manifestations are described by Tillman.<sup>428</sup> Prodromal symptoms, occurring within thirty-nine to one hundred days from the day of first possible exposure, consisted of fever, cough, weakness and malaise, urticarial eruption, headache, abdominal pain, pain in the chest, chills and diarrhea. In every instance there was a lucid interval of eleven to twenty-eight days between these symptoms and the onset of neurologic disturbances. Usually the cerebral phase began insidiously, but occasionally it was abrupt. Aphasia, amnesia, blocking, confusion, disorientation, defective memory and coma were outstanding. Spasticity, occasional early flaccidity changing to spasticity, rigidity, hyperreflexia, pathologic reflexes and loss of superficial reflexes were common to all patients. In 5 cases transient disturbances of the third, fourth and sixth cranial nerves were present, and in 2 there was questionable involvement of the facial nerve. Motor paralysis was characteristic, involving one or more limbs, but a lesion of the lower motor neuron was not observed. Sensation was not affected.

Lippincott and his associates<sup>429</sup> studied the effect of treatment with antimony. Of 33 patients given "fuadin" 27 (82 per cent) were again passing eggs within three months or less. These 27 were again treated with "fuadin"; 24 were passing eggs again in three months' time or less. Of 59 patients treated with tartar emetic, 11 (19 per cent) were passing eggs within three months or less. Both drugs produced an average plasma antimony level of about 100 micrograms per liter after 0.75 Gm. of antimony had been given in about five weeks' time; the concentration at all

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427. Winkenwerder, W. L.; Hunninen, A. V.; Harrison, T.; Billings, F.; Tremains, C.; Douglas, G., and Maier, J.: Studies on Schistosomiasis Japonica: II. Analysis of Three Hundred and Sixty-Four Cases of Acute Schistosomiasis with Report of Results of Treatment with Fuadin in One Hundred and Eighty-Four Cases, *Bull. Johns Hopkins Hosp.* **79**:406-435, 1946. Mason, P. K.; Daniels, W. B.; Paddock, F. K., and Gordon, H. B.: Latent Phase of Asiatic Schistosomiasis, *Arch. Int. Med.* **78**:662-678 (Dec.) 1946.

428. Tillman, A. J. B.: Schistosomiasis Japonica with Cerebral Manifestations: Report of Seven Cases, *Arch. Int. Med.* **79**:36-61 (Jan.) 1947.

429. Lippincott, S. W.; Ellenbrook, L. D.; Rhees, M., and Mason, P.: A Study of the Distribution and Fate of Antimony When Used as Tartar Emetic and Fuadin in the Treatment of American Soldiers with Schistosomiasis Japonica, *J. Clin. Investigation* **26**:370-378, 1947.



stages was higher in the cells than in the plasma. For several hours after administration of the drug, a higher concentration in the blood cells was found in the group given tartar emetic than in the group given "fuadin." Since the adult worms are known to infest erythrocytes, the question is raised whether the higher blood cell concentration of antimony obtained with tartar emetic may not be responsible for the superior therapeutic efficiency of this drug as compared with "fuadin."

#### APPENDIX

*Arterial Supply.*—Careful dissections in 60 injected cadavers revealed a single appendical artery in 42; in only 19 did the course correspond with the description found in textbooks.<sup>430</sup>

*Appendicitis.*—Bohrod<sup>431</sup> points out that the development of appendical lymphoid tissue, with narrowing of the lumen, closely parallels the incidence of acute appendicitis with respect to the characteristic age and sex distribution. The lymphoid tissue reaches its maximum development in the first decade and is better developed in the male. When the muscularis fully develops in the second decade, the lumen becomes small. Appendicitis results from obstruction of the lumen. Moses<sup>432</sup> reports that traction on the appendix or distention of the lumen will reproduce the cramping, poorly localized pains characteristic of early appendicitis. Early appendicitis is regarded as a miniature "blind loop" form of intestinal obstruction. If the obstruction is not relieved, venous congestion ensues, with the outpouring of an exudate into the lumen and the wall and around the exterior of the appendix; persistence of this process results in arterial occlusion, with resultant perforation or gangrene.

Kay and Lockwood,<sup>433</sup> in a study of experimental appendical peritonitis, found that there were no quantitative hematologic changes of prognostic significance although alterations in the prothrombin time were of suggestive value.

In a series of cases reported by Tashico and Zinninger<sup>434</sup> the average delay in hospitalization for acute unruptured appendicitis was 26.6 hours; for acute appendicitis with perforation it was 75.6 hours. The mortality

430. Shah, M. A., and Shah, M.: The Arterial Supply of the Vermiform Appendix, *Anat. Rec.* **96**:457-460, 1946.

431. Bohrod, M. G.: The Pathogenesis of Acute Appendicitis, *Am. J. Clin. Path.* **16**:752-760, 1946.

432. Moses, W. R.: Appendicitis: A Clinico-Pathological Study, *South. M. J.* **39**:902-906, 1946.

433. Kay, J. H., and Lockwood, J. S.: Experimental Appendiceal Peritonitis: I. The Prognostic Significance of Certain Hematologic Factors, Especially the Prothrombin Time, *Surgery* **20**:56-71, 1946.

434. Tashico, S., and Zinninger, M. M.: Appendicitis: A Review of Nine Hundred and Thirty-Six Cases at the Cincinnati General Hospital, *Arch. Surg.* **53**:545-563 (Nov.) 1946.

rate was 5.3 per cent among Negroes and 2.6 per cent among white persons.

Hurwitt<sup>435</sup> emphasizes the need for laparotomy in the presence of persisting signs and symptoms ordinarily associated with acute appendicitis despite the preexistence or coexistence of other diseases that may produce abdominal complaints, such as pneumonia, tonsillitis, infections of the upper respiratory tract, mastoiditis, chronic glomerulonephritis, myocardial infarction, inguinal hernia, diabetes mellitus and syphilis of the central nervous system.

Simpson<sup>436</sup> discusses the clinical features of acute appendicitis in persons over 60 years of age. The mortality rate for this group is approximately 25 to 30 per cent.

Intestinal obstruction roentgenologically simulating cancer of the rectosigmoid proved at operation to be due to appendicitis with pelvic peritonitis.<sup>437</sup>

In a group of 50 cases of appendical peritonitis, treated without drainage and with immediate appendectomy in 22, the administration of 100,000 units of penicillin every two hours for several days resulted in the recovery of all but 1 patient.<sup>438</sup>

In an analysis of 5,540 cases of acute appendicitis at Cook County Hospital since 1928, Meyer, Requarth and Kozoll<sup>439</sup> found that from 1928 to 1932 the mortality rate was 1.1 per cent when perforation had not occurred and from 1944 to 1945 it was 0.78 per cent. When perforation had occurred, it was 26.4 per cent in the earlier period and 13.9 per cent in the later one, the reduction being attributed chiefly to chemotherapy. In cases of acute appendical abscess the nonoperative (Ochsner) treatment yielded results much superior to those obtained by the operative treatment, the mortality rates being 18 and 4.2 per cent respectively in the early period and 8.5 and 3.1 per cent in the later period. Jackson<sup>440</sup> reports 15 cases of perforative appendicitis with peritonitis or abscess formation in which the appendix was removed, sulfathiazole employed intraperitoneally and the incision closed without drainage; there were no deaths, although a secondary intraperitoneal abscess in 1 case required

435. Hurwitt, E. S.: Acute Appendicitis Occurring During the Course of Other Diseases, *New England J. Med.* **236**:20-23, 1947.

436. Simpson, D. G.: Acute Appendicitis in the Aged, *Brit. M. J.* **2**:986-989, 1946.

437. Courty, M. A.: Pseudo-cancer recto-sigmoïdien du a une appendicite pelvienne, *Arch. d. mal. de l'app. digestif* **35**:74-77, 1946.

438. Crile, G., Jr.: Peritonitis of Appendiceal Origin Treated with Massive Doses of Penicillin, *Surg. Gynec. & Obst.* **83**:150-162, 1946.

439. Meyer, K. A.; Requarth, W. H., and Kozoll, D. D.: Progress in the Treatment of Acute Appendicitis, *Am. J. Surg.* **72**:830-840, 1946.

440. Jackson, A. S.: Non-Drainage and Early Ambulation in Cases of Perforative Appendicitis, *Arch. Surg.* **54**:644-655 (June) 1947.

drainage. The treatment of peritonitis is further discussed by Crile<sup>441</sup> and by Brown.<sup>442</sup>

Streptomycin is given the credit for a dramatic recovery from peritonitis caused by a colon bacillus subsequent to ureterolithotomy in a patient with ureteral calculi and a purulent renal infection due to *Escherichia coli*. The condition was not influenced by the administration of sulfonamide drugs and penicillin.<sup>443</sup> Bacilli apparently were fully eliminated from the peritoneal cavity but not from the urinary tract, although there was no obstruction.

*Mucocele*.—A mucocele of the appendix suspected clinically and diagnosed roentgenologically was found at operation.<sup>444</sup> Miller<sup>445</sup> reports 5 cases in which a mucocele of the appendix was originally diagnosed as appendicitis; perforation occurred in another instance.<sup>446</sup>

*Taenia Saginata*.—Two cases in which *Taenia saginata* were present in the appendix are described.<sup>447</sup>

*Carcinoid*.—Of 29 carcinoids of the appendix, metastatic lesions were found in 3.<sup>448</sup> Early removal is more frequent than in carcinoid of the stomach because on account of the symptoms of appendicitis the appendix is removed; the diagnosis is often overlooked.

*Carcinoma*.—A primary adenocarcinoma of the appendix was associated with the development of a mucous fistula.<sup>449</sup>

#### COLON

*Parasympathetic Innervation*.—Lannon and Weller,<sup>450</sup> in a study of the nerve supply to the distal half of the large intestine in 9 infants and 9 adults (all Bantu), state that the parasympathetic nerves arise from the

441. Crile, G., Jr.: Peritonitis, *Am. J. Surg.* **72**:859-864, 1946.

442. Brown, M. J.: Combined Penicillin and Sulfonamide Treatment of Peritonitis, *Am. J. Surg.* **73**:56-61, 1947.

443. Muellner, S. R., and Rutenberg, A.: The Use of Streptomycin in Colon Bacillus Peritonitis, *New England J. Med.* **235**:327-328, 1946.

444. Euphrat, E. J.: Roentgen Features of Mucocele of the Appendix, *Radiology* **48**:113-117, 1947.

445. Miller, D.: Mucocele and Myxoglobulosis of the Appendix, *S. Clin. North America* **27**:337-343, 1947.

446. Longo, O. F.: Mucocele apendicular perforado, *Bol. y trab., Acad. argent. de cir.* **30**:863-870, 1946.

447. Clark, H. C.: *Taenia Saginata* in the Appendix, *Am. J. Surg.* **7**:128-129, 1946. Rossi, A. A., and Bruzzoni, N. R.: A Case of Appendicitis Caused by *Taenia Saginata*, *Prensa méd. argent.* **33**:2085-2086, 1946.

448. D'Ingianni, V.: Carcinoid of the Appendix with Metastasis, *New Orleans M. & S. J.* **99**:158-161, 1946.

449. Crile, G. and Glenn, C. G.: Primary Adenocarcinoma of the Appendix with Development of Mucus Fistula, *U. S. Nav. M. Bull.* **47**:328-330, 1947.

450. Lannon, J., and Weller, E.: The Parasympathetic Supply of the Distal Colon, *Brit. J. Surg.* **34**:373-376, 1947.

second and third sacral segments and are distributed directly to the rectum and the descending colon. They communicate with the hypogastric plexuses but do not follow the paths of the blood vessels. The authors point out that in the application of these results in operations on the colon periarterial stripping of the inferior mesenteric artery should not lead to parasympathetic dysfunction of the colon and that resection of the rectum and the lower pelvic colon should not destroy the parasympathetic supply to the colon.

*Hepatodiaphragmatic Interposition.*—Starr<sup>451</sup> reports the roentgenologic demonstration of colon between the liver and the diaphragm.

*Megacolon.*—The clinical and roentgenologic features and the early development of megacolon in the newborn are described by Ehrenpreis.<sup>452</sup> The process is apparently due to a disturbance of innervation; improper evacuation is considered primary and dilatation secondary.

Twenty-eight cases of primary megacolon observed in the past twenty-five years at the Lahey Clinic are described by Swarts.<sup>453</sup> In 20 it was congenital, in 2 acquired and in 6 indeterminate. The most constant symptoms were constipation and abdominal pain. Twenty-one patients were managed medically, with good results in 16. Seven patients were subjected to sympathectomy, colectomy or both, with excellent results in only 1. Sympathectomy has been disappointing; colectomy is considered the procedure of choice if medical management fails. The regular use of enemas and the avoidance of laxatives are outlined as basic principles of treatment. Impactions are a constant source of trouble, for which small enemas of magnesium, glycerin and water are recommended. Mecholyl bromide, 0.1 to 0.2 Gm., may be occasionally of benefit.

Scott and Serenati<sup>454</sup> present a somewhat different view, dividing megacolon into four types for which diverse therapeutic procedures are indicated: congenital organic obstruction requiring some type of plastic procedure, neurogenic dysfunction responding diagnostically and therapeutically to spinal anesthesia or requiring lumbar sympathectomy, functional obstruction (abnormal length of sigmoid) relieved by resection of the redundant loop with or without sympathectomy and extrinsic metabolic difficulties necessitating replacement therapy. However, these authors agree that most patients should first be subjected to a conservative medical regimen consisting of colonic irrigations, mineral oil, mild catharsis in rare instances, low roughage diet and drugs.

451. Starr, E.: Hepatodiaphragmatic Interposition of the Colon with Gastric Hypertrophy, *Am. J. Roentgenol.* **56**:22-26, 1946.

452. Ehrenpreis, T.: Megacolon in the Newborn: A Clinical and Roentgenological Study with Special Regard to the Pathogenesis, *Acta chir. Scandinav.* 1946, supp. 112, pp. 1-403.

453. Swarts, J. M.: Primary Megacolon, *Gastroenterology* **8**:519-525, 1947.

454. Scott, W. J. M., and Serenati, O. J.: Megacolon: Mechanisms and Choice of Treatment, *Surgery* **20**:603-618, 1946.

*Functional Disorders.*—Prolonged proctoscopic observations were made by Almy and Tulin<sup>455</sup> on 7 healthy young men. When under stress from mechanically produced headache or from pain caused by immersion of the forearm in ice water, the subjects manifested a bodily reaction comprising hypertension, sweating, sighing, pallor of the skin and changes in colonic function. Increased motor activity of the lower part of the sigmoid was regularly present; significant engorgement of the mucosa was usually seen and occasionally an increased secretion of mucus. These phenomena appeared to be independent of the quality of the emotional reactions of the subject. The emotional conflicts consisted of resentment toward the experimenters, concern about self preservation, desire to comply and self reproach. Nausea, usually associated with spasm of the sigmoid, was absent in 2 subjects predominantly resentful.

The psychosomatic aspects of gastrointestinal disorders are discussed by a number of writers.<sup>456</sup> Dakin points out that lack of special psychiatric training or of time should not deter the physician from learning the emotional disturbances in every patient and from treating these factors with psychologic technics.

Functional gastrointestinal disorders accounted for a large part of the disability from medical causes in the United States Army.<sup>457</sup> Hospitalization, with prolonged investigation and medical treatment, had an adverse effect. Prompt and direct attention to the personality disturbance, with a minimum of emphasis on medical study and organic therapy, resulted in a significant saving in manpower, a considerable decrease in hospitalization and great benefit to the patients. The reviewers agree in principle but they are reluctant to minimize the importance of medical study; both types are important.

*Ulcer of the Cecum.*—A benign ulcer of the cecum clinically simulated appendicitis. At operation a malignant growth was suspected, and a hemicolectomy was performed.<sup>458</sup> Ileocolic intussusception occurred at the site of a nonspecific cecal ulcer.<sup>459</sup>

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455. Almy, T. P., and Tulin, M.: Alterations in Colonic Function in Man Under Stress, Experimental Production of Changes Simulating the "Irritable Colon," *Gastroenterology* 8:616-626, 1947.

456. Dakin, M. J.: The Psychosomatic Approach in General Practice, *M. Clin. North America* 31:213-222, 1947. Paster, S.: General Aspects of Psychosomatic Medicine, *Rev. Gastroenterol.* 14:391-402, 1947. Savitt, R. A.: Gastrointestinal Disorders in Military and Civilian Life, *ibid.* 14:402-409, 1947. Portis, S. A.: The Gastroenterological Aspects of Psychosomatic Medicine, *ibid.* 14:409-419, 1947. Gibb, W. T., Jr.: Functional Derangement of Digestion, *Am. Pract.* 1:542-548, 1947.

457. Halsted, J. A.: Functional Gastrointestinal Disorders: Lessons Learned from Military Medicine, *New England J. Med.* 235:747-754, 1946.

458. Cromar, C. D. L.: Benign Ulcer of the Caecum, *Am. J. Digest. Dis.* 13:230-232, 1946.

459. Blum, L.: Nontumid Ileocolic Intussusception in an Adult: Report of a Case with Cecal Ulcer, *S. Clin. North America* 17:355-360, 1947.

*Volvulus.*—According to Gardiner,<sup>460</sup> volvulus of the cecum is far more common than has hitherto been supposed. In 50 per cent of the cases it occurs in patients between the ages of 20 and 40, but the process is frequently found in older persons. Males seem to be more often affected than females, the proportion being 3 to 1. Failure of the normal fixation of the cecum and persistence of its mesentery leave the cecum and the ascending colon with a variable degree of mobility and liable to torsion. Exertion and strenuous occupations are precipitating factors; other exciting causes include trauma, pregnancy, dietetic errors, gaseous distention and violent purgation. The usual symptoms are pain and tenderness in the right iliac fossa shifting to the center of the abdomen, with immediate or subsequent gaseous distention and obstruction; the temperature and pulse often remain normal throughout. A plain roentgenogram of the abdomen is of great value and often establishes the diagnosis. Treatment consists of laparotomy, with derotation and fixation if the intestine is viable or with hemicolectomy if it is gangrenous. Volvulus of the sigmoid, an uncommon cause of intestinal obstruction, usually occurs only if the sigmoid is dilated, long and redundant.<sup>461</sup> Demonstration of a corkscrew-like arrangement of the mucosa in spot roentgenograms is pathognomonic.

*Diverticulosis and Diverticulitis.*—Several papers have appeared.<sup>462</sup> Anderson<sup>462b</sup> describes an instance of cecal diverticulitis with perforation and peritonitis, the hundredth case to be reported. The patient recovered after closure of the diverticulum and sulfonamide therapy. Ballinger<sup>462c</sup> reviews gastrointestinal roentgenologic examinations made in 1,000 consecutive cases. Diverticula were present in 115 (11.5 per cent); in 98 (9.8 per cent) they were in the colon, in 16 (1.6 per cent) in the duodenum and in only 1 (0.1 per cent) in the esophagus. Of the 98 cases of colonic diverticula, evidence of diverticulitis was present in 25.

Morton<sup>462d</sup> describes the typical clinical picture of diverticulitis: a corpulent sedentary person, middle aged or older, with a history of constipation, is seized suddenly with cramping, colicky pain in the lower abdomen, diarrhea and increasing constipation. This is frequently fol-

460. Gardiner, R. H.: Volvulus of the Caecum, *Brit. M. J.* **1**:83-87, 1947.

461. Ritvo, M., and Golden, J. L.: The Roentgen Diagnosis of Volvulus of the Sigmoid with Intestinal Obstruction, *Am. J. Roentgenol.* **56**:480-488, 1946.

462. (a) Galambos, A., and Mitelmann-Galambos, W.: Diverticulosis and Diverticulitis of the Colon, *Rev. Gastroenterol.* **13**:171-194, 1946. (b) Anderson, L.: Perforated Diverticula of the Cecum with Peritonitis, *Proc. Staff Meet., Mayo Clin.* **21**:465-469, 1946. (c) Ballinger, W. M.: Diverticula of the Digestive Tract, *South. M. J.* **39**:897-902, 1946. (d) Morton, J. J., Jr.: Diverticulitis of the Colon, *Ann. Surg.* **124**:725-745, 1946. (e) Schlotthauer, H. L.: Familial Diverticulosis of the Colon: Report of Seven Cases in One Family of Nine Persons, *Ann. Surg.* **124**:497-502, 1946. (f) Cohen, S. E., and Matthews, B. L.: Dissecting Diverticulitis of the Colon, *Surgery* **20**:823-827, 1946.

lowed by nausea, vomiting, distention, fever and tenderness in the lower quadrants, usually the left, where a mass often is palpable. Moderate leukocytosis is the rule. About 20 per cent have occult blood in the stool. The complications include obstruction, abscess, perforation, peritonitis and formation of fistula. In 17 of 111 patients carcinoma was also present. There were 39 perforations, with 12 deaths. Diverticulitis with spasm is a self-limiting disease, necessitating only rest, supportive therapy and dietary restriction in most instances. Proximal colostomy occasionally may be necessary. Diverticulitis with complications almost invariably is a serious disorder, demanding expert surgical intervention.

Diverticulosis of the colon was found in all the male members of a white family of 9 (7 brothers and 2 sisters) of ages ranging from 49 to 68 years.<sup>462e</sup> A type of diverticulum of the colon is described which begins as a herniation of the lumen into the wall of the bowel and burrows its way along the wall, termed "dissecting intramural diverticulitis."<sup>462f</sup>

*Ulcerative Colitis.*—In an excellent article, Ginsberg and Ivy<sup>463</sup> critically review the evidence pertaining to the cause of the disease. Acute lesions of the colon have been produced by the intravenous injection of diplostreptococci, streptococci, *B. coli*, *Bacillus dysenteriae* and presumably a virus. Cook has shown experimentally that acute ulcers may be produced and maintained or relapses elicited by apical dental infections, using the diplostreptococcus of Bargaen. This work has not been repeated. Observations on *Bacillus necrophorum* suggest that it may play a role in the chronicity of the disease. Mechanical trauma, vascular injuries caused by contraction of the muscularis or by capillary poisons, sclerosing solutions or allergenic substances may cause acute lesions tending to heal rapidly. The colitides of tuberculosis, amebiasis, bacillary dysentery and lymphogranuloma are separate entities. Though emotional factors may play a role in exacerbation of symptoms and may be related to the onset of the disease, there is a paucity of evidence showing that ulcerative colitis is the end result of functional, vascular or neurotropic disturbance.

In a comparative clinical study of 22 cases of regional enteritis and 67 cases of idiopathic ulcerative colitis, Weinberg and his associates<sup>464</sup> noted no significant difference in the age distribution or the sex incidence. Hemorrhage was the first manifestation in a case of acute ulcerative colitis.<sup>465</sup> Proctoscopic examination was not diagnostic, but roentgen studies revealed a narrowed descending colon and sigmoid, with pronounced distortion of the mucosal pattern.

463. Ginsberg, R. S., and Ivy, A. C.: The Etiology of Ulcerative Colitis: An Analytical Review of the Literature, *Gastroenterology* 7:67-90, 1946.

464. Weinberg, B. J.; Sorter, H., and Necheles, H.: Regional Enteritis and Idiopathic Ulcerative Colitis: A Clinical Study, *Am. J. Digest. Dis.* 13:346-350, 1946.

465. Jobb, E.: Unusual Initial Onset of Ulcerative Colitis with Exsanguinating Bowel Hemorrhage, *Gastroenterology* 7:483-488, 1946.

A case of acute fulminating colitis, with peritonitis, extensive loss of the bowel wall and death five weeks after the onset, is reported;<sup>466</sup> therapy had consisted of the administration of plasma, blood, sodium sulfadiazine and large quantities of solutions containing sodium chloride and sugar. Five similar cases from the literature are analyzed; all the patients died in less than nine weeks. Exploratory operation had been performed in all, including ileostomy, suture of a perforation, drainage of an abscess, cecostomy and appendicostomy in individual cases.

Ricketts and Palmer,<sup>467</sup> reporting an incidence of one or more complications in 31 per cent of 206 cases, classify the complications into five groups: (1) those involving the colon itself, (2) those involving adjacent structures, (3) those distant from the colon, (4) those resulting from deficient nutrition and (5) a miscellaneous group. The complications in the first group included polyps in 21, stricture in 8, obstruction in 6 and carcinoma in 3. Hemorrhage occurred frequently, but there was no fatality from this. In the second group internal or external fistulas were found in 9 and perforation with peritonitis in 7. Complications distant from the colon were lesions of the skin and mucosal surface in 22, arthritis in 12, venous thromboses in 4, hepatitis in 1 and septic infection in 27. There were 3 cases of infantilism in a subgroup of 23 children. Peripheral neuritis was observed in 3 patients.

Anemia was present in 71 of 109 cases reported by Pollard and others,<sup>468</sup> it was hypochromic and microcytic in 58 and normocytic in 13. Many factors apparently contributed to the development of the anemia, including chronic hemorrhage, inadequate intake or defective absorption of food, deficient nutrition, toxemia and exacerbations of the disease.

Five instances of hepatic cirrhosis, observed by Tumen and others<sup>469</sup> among 151 cases of ulcerative colitis, were attributed to nutritional deficiencies (anorexia, hypermotility, poor absorption and loss in rectal discharges), with absorption of toxic substances as a possible additional factor.

Cattell and Boehme,<sup>470</sup> emphasizing the importance of malignant degeneration, found approximately 75 cases in a review of the literature

466. Chisholm, T. C.: Acute Fulminating Ulcerative Colitis with Massive Perforation and Peritonitis, *Arch. Surg.* **53**:462-476 (Oct.) 1946.

467. Ricketts, W. E., and Palmer, W. L.: Complications of Chronic Non-Specific Ulcerative Colitis, *Gastroenterology* **7**:55-66, 1946.

468. Pollard, H. M.; Block, M. and Bachrach, W. H.: Causes and Management of Anemia Associated with Chronic Ulcerative Colitis, *J. A. M. A.* **134**:341-346 (May 24) 1947.

469. Tumen, H. J.; Monaghan, J. G., and Jobb, E.: Hepatic Cirrhosis as a Complication of Chronic Ulcerative Colitis, *Ann. Int. Med.* **26**:542-553, 1947.

470. Cattell, R. B., and Boehme, E. J.: The Importance of Malignant Degeneration as a Complication of Chronic Ulcerative Colitis, *Gastroenterology* **8**:695-710, 1947.



and described 9 additional instances. The lesions are highly malignant and metastasize early. The average duration of symptoms before the diagnosis of a malignant process was nine years. The lesions were in the cecum in 1, in the hepatic flexure in 1, and in the rectum and rectosigmoid in 7. Histologically, there were three adenocarcinomas, three carcinomas of the simplex type and three mucinous carcinomas. All 9 patients were subjected to operation; 4 underwent a resection, palliative only in 2 instances since local or distant metastasis was present. There were no operative deaths; the 2 patients without metastasis are living and well five and one-half years and twenty months respectively after operation. The other 7 patients died from various causes.

By means of "biographic anamnesis," a detailed life history was obtained from 6 patients with ulcerative colitis which demonstrated that the onset of the disease and its recurrences were related to emotional trauma resulting in a specific internal conflict.<sup>471</sup> The author formulates this conflict as an acute love loss, combined with humiliation and a feeling of inferiority, and regards it as the cause of the colitis. Four of the 6 patients improved after supportive psychotherapy.

West<sup>472</sup> reports 3 cases relieved by brief psychotherapy and discusses the principles of such treatment. The experiments of Lium and Porter (1939) wherein colonic ulcerations were produced in twenty-four hours by sustained colonic muscular spasm and healing induced after relaxation for ten to fourteen days are recalled. It is hypothesized that in some cases of ulcerative colitis anxiety causes muscular spasm and mucosal changes in an organ previously rendered susceptible by either a psychological or a physical sensitization or both. While the diarrheal response to frank anxiety is well known, much of the anxiety of these patients is unconscious. Deep anxiety over problems of emotional aggressiveness characterizes ulcerative colitis.

Of 55 patients treated with succinylsulfathiazole and observed for two years, 74.5 per cent had a complete remission of symptoms, 7.3 per cent improved and 18.2 per cent did not improve.<sup>473</sup> Thirty-nine patients (71 per cent) had no complicating toxic or systemic manifestations, and thus their condition was classified as mild. It was in this group that most of the remissions occurred.

Thirty-seven patients with ulcerative colitis were treated with 2-(p-nitro-benzenesulfonamido)-thiazole, or nisulfazole, in doses of 4 to 6

471. Groen, J.: Psychogenesis and Psychotherapy of Ulcerative Colitis, *Psychosom. Med.* 9:151-174, 1947.

472. West, R.: Psychotherapy of Ulcerative Colitis, *Lancet* 2:899-903, 1946.

473. Collins, E. N., and Hewlett, J. S.: Succinyl Sulfathiazole (Sulfasuxidine) in the Treatment of Chronic Ulcerative Colitis: A Report of Fifty-Five Cases Followed Two Years; Its Value by Retention Enema in Early Cases, *Gastroenterology* 7:549-554, 1946.

Gm. initially, gradually reduced to 1 to 2 Gm. daily.<sup>474</sup> Thirty-four patients were reported to have recovered, i.e., to be symptom free and passing not more than two to three well formed stools daily; 3 were improved. Ten known relapses occurred, four of these during an infectious disease. No untoward effects were observed in patients taking 1 to 2 Gm. daily for several months; 2 patients took 2 Gm. daily for seventeen and twenty months respectively.

The use of sulfonamide drugs and antibiotics is discussed comprehensively by Bargaen.<sup>475</sup> Azosulfamide ("neoprontosil") is considered the most effective drug in chronic ulcerative colitis, although toxic reactions occur. Sulfathiazole, sulfadiazine, sulfaguanidine, succinylsulfathiazole ("sulfasuxidine") and phthalylsulfathiazole ("sulfathaladine") have been found effective in selected cases. The administration of several of the sulfonamide drugs may be more effective than the use of one alone. The best results with penicillin have been obtained in the acute fulminating forms; perhaps the doses, already large, should be even greater. In the few patients to whom streptomycin was administered preliminary results were not encouraging.

Improvement apparently occurred in 3 patients after thiouracil had been given and in 1 after methyl thiouracil.<sup>476</sup>

Twenty-one patients with ulcerative colitis were treated with preparations of small intestinal mucosa of the hog.<sup>477</sup> Two dried preparations are compared; one in which enzymal activity was retained proved ineffective, and the other caused apparent remission of symptoms in 9 cases. The physiologic basis for this therapy is obscure. The authors wisely point out that the evaluation of any therapy in this disease is difficult and requires a careful assessment of adequate control data.

Lahey<sup>478</sup> recommends early ileostomy for patients not responding to medical management. The mortality rate in his experience has been reduced from 26 to 2 per cent. Cave<sup>479</sup> reports that among 101 patients with intractable ulcerative colitis treated surgically by ileostomy and by partial or complete colectomy there were twenty immediate or early fatalities. Of the 81 survivors, 50 have been followed over a period

474. Major, R. H.: The Nisulfazole Treatment of Chronic Ulcerative Colitis, *Am. J. M. Sc.* **1**:485-490, 1946.

475. Bargaen, J. A.: The Use of the Newer Sulfonamides and Antibiotics in Intestinal Diseases, *M. Clin. North America* **30**:919-931, 1946.

476. Martin, L.: Treatment of Ulcerative Colitis with Thiouracil, *Lancet* **2**:944-946, 1946.

477. Gill, A. M.: Treatment of Ulcerative Colitis with Intestinal Mucosa, *Proc. Roy. Soc. Med.* **39**:512-519, 1946.

478. Lahey, F. H.: Earlier Ileostomy in Severe Ulcerative Colitis, *Surg., Gynec. & Obst.* **85**:230-232, 1947.

479. Cave, H. W.: Late Results in the Treatment of Ulcerative Colitis, *Ann. Surg.* **124**:716-724, 1946.

ranging from one to ten years. The fecal stream has been successfully reestablished in 2 patients by ileosigmoidostomy. Eleven patients underwent primary ileosigmoidostomy; lesions of the terminal ileal segment, requiring further resection developed in 2 patients, 1 of whom died. Acute ileus and ileal prolapse were not infrequent complications. Sudden collapse from loss of salt occasionally occurred. Forty of the patients are leading an active, useful life.

Crohn and his associates<sup>480</sup> comprehensively review 77 cases of so-called right-sided colitis. The age distribution was similar to that in usual ulcerative colitis or ileitis. The average age was 27.3 years; the youngest patient was 6 and the oldest 60 years of age. There were 45 women and 32 men. Pure "right-sided colitis" involving the cecum and the ascending colon was observed in 22 instances. The transverse colon and the descending colon alone were regionally involved in 16 cases. In the remaining 39 cases the proximal colon from the cecum to the sigmoid was involved either continuously or intermittently by "skip" lesions. Associated involvement of the terminal end of the ileum was noted in 33 cases. Intestinal obstruction occurred in 2, fistula in 15, perirectal abscesses without fistulas in 4, internal fistula in 1 and fecal fistulas opening on the abdominal wall in 2. Fever was the most outstanding general manifestation of the disease, being present in 49 of the 77 cases. Monoarticular, but more commonly polyarticular, involvement was frequent. The prognosis of "right-sided colitis" is considered "good," with a survival rate of 84 per cent. Among 55 patients treated surgically there were 9 deaths. Of the 46 surviving operation, only 3 experienced subsequent involvement of the rectum and required ileostomy; 2 of these died. The authors regard segmental colitis as an entity different from ulcerative colitis in its clinical course, its manifestations and its response to surgical therapy.

*Lymphopathia Venereum.*—The etiology, symptoms, diagnosis and treatment are discussed by Wright, Freeman and Bolden.<sup>481</sup> In the pre-stricture stage sulfonamide compounds seem to have some beneficial effect, but it is doubtful if drugs can permanently prevent extension of the process in all cases. Penicillin has not been of value. Surgical treatment is necessary once a fibrous stricture of any considerable extent has developed. Five instances of carcinoma superimposed on the granulomatous lesion are described in addition to 27 case histories. Savignac<sup>482</sup> reports complete rectal obliteration.

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480. Crohn, B. B.; Garlock, J. H., and Yarnis, H.: Right-Sided (Regional) Colitis, *J. A. M. A.* **134**:334-338 (May 24) 1947.

481. Wright, L. T.; Freeman, W. A., and Bolden, J. V.: Lymphogranulomatous Strictures of the Rectum, *Arch. Surg.* **53**:499-544 (Nov.) 1946.

482. Savignac, M. R.: Un nouveau cas d'obliteration complete d'une stenose inflammatoire du rectum, *Arch. d. mal. de l'app. digestif.* **35**:77-80, 1946.

*Polyps.*—During a nineteen month period, 1,031 women who considered themselves well submitted to sigmoidoscopic and roentgenologic examinations.<sup>483</sup> Nineteen polyps were found in 18 persons. No symptoms characterized the group; none of the 19 polyps was palpable by rectal examination or visible after a barium enema. Microscopic sections of tissue taken from these lesions were studied independently by three pathologists; complete agreement was recorded in regard to only three specimens. Polypoid disease of the colon, according to Buie,<sup>484</sup> is of two main types: (a) discrete polypoid outgrowths, usually sessile, with normal intervening mucosa and (b) a diffuse hyperplastic involvement, with polyps of all types, sizes and shapes.

In a study of the incidence and distribution of adenomas of the large intestine in 1,460 consecutive autopsies, Helwig<sup>485</sup> found that the incidence increases with age, reaching a maximum (24 per cent) in the eighth decade. The over-all incidence in Negroes was 2.7 per cent and that in white patients 10.5 per cent. Adenomas were slightly more frequent in men than in women. A single adenoma was found in 80 of 139 patients, and two or more tumors were noted in the rest. Adenomas are considered true neoplasms rather than a reaction to a diffuse inflammatory process. Swinton<sup>486</sup> shares this opinion.

Generalized polyposis of the colon in a woman aged 22 was treated, in sequence, by electrocoagulation of polyps, ileosigmoidostomy and partial colectomy.<sup>487</sup> Rectal hemorrhages recurred three years later, necessitating a two stage resection of the colon and rectum. Microscopic examination revealed malignant degeneration of two of the polypi. Copello and Ramos Mejia<sup>488</sup> report a multiple polyposis involving both the small and the large intestine.

Dixon and Benson<sup>489</sup> treated most of their 19 patients with polypoid disease by performing ileosigmoidostomy at the first stage and subsequently by fulguration of the remaining polypi in the rectum and rectosigmoid.

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483. Ortmyer, M.: Biologic Characteristics of Non-Palpable, Non-Symptomatic Solitary Polyps of the Rectum, *J. Nat. Cancer Inst.* 7:387-393, 1947.

484. Buie, L. A.: Remarks Concerning Malignant Lesions, Polypoid Disease and Diverticula of the Terminal Portion of the Large Intestine, *S. Clin. North America* 26:968-980, 1946.

485. Helwig, E. B.: The Evolution of Adenomas of the Large Intestine and Their Relation to Carcinoma, *Surg. Gynec. & Obst.* 84:36-49, 1947.

486. Swinton, N. N.: The Significance of Mucosal Polyps of the Colon and Rectum, *S. Clin. North America* 27:675-680, 1947.

487. Charrier, J.; Hillemand, J., and Hartman, L.: Treatment of Generalized Essential Rectocolic Polyposis, *Arch. d. mal. de l'app. digestif* 36:5-16, 1947.

488. Copello, O., and Ramos Mejia, M. M.: Poliposis difusa del intestino delgado y del grueso, *Bol. y trab., Acad. argent. de cir.* 30:635-646, 1946.

489. Dixon, C. F., and Benson, R. E.: Total and Subtotal Colectomy with Review of Seventy-Two Cases, *S. Clin. North America* 26:949-967, 1946.

*Lipoma.*—Runyeon<sup>490</sup> reports 2 submucous lipomas and reviews 121 similar ones. Two submucous lipomas originating in the ileocecal valve and in the ascending colon produced intermittent intussusception.<sup>491</sup> A subserous lipoma grossly simulated carcinoma.<sup>492</sup>

*Carcinoma.*—McLaughlin<sup>493</sup> describes carcinoma of the cecum in association with acute appendicitis, the twelfth instance to be recorded in the literature.

The sex incidence in 50 cases of carcinoma of the cecum was approximately uniform.<sup>494</sup> The average age was 47.8 years, the youngest patient being 19 and the oldest 72. The average duration of symptoms before operation was 10.1 months. Pain was present in 92 per cent and was the first symptom in 74 per cent. It was located in nearly all cases in the right lower abdominal quadrant, beginning usually as a dull ache and progressing to a cramping colicky pain. Weight loss was pronounced in 46 per cent, the average loss being 25 pounds (11.3 Kg.). Constipation and diarrhea were noted in 8 patients; some change in bowel habits occurred in 38 per cent. Ten per cent of the patients noted a mass in the right lower quadrant before presenting themselves for examination; in 2 the mass was the first indication of the disease. Anemia was a presenting complaint in 4, all having been previously treated with iron and liver.

Cole<sup>495</sup> presents evidence that earlier diagnosis, better preoperative and postoperative care and improved surgical technics have decreased the mortality rate. However, antibiotics are not a substitute for careful surgical treatment.

Forty-eight authentic cases of carcinoma of the large bowel, excluding the rectum and sigmoid, in patients 16 years of age or less are reviewed by Johnston.<sup>496</sup> Colloid carcinoma is ten times more frequent in children; hence palpable masses are commonly found. A carcinoma of the transverse colon in a 15 year old boy is reported.<sup>497</sup>

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490. Runyeon, F. G.: Submucous Lipoma of the Colon, *New York State J. Med.* **46**:2272-2276, 1946.

491. Pack, G. T., and Booher, R. J.: Intussuscepting Submucous Lipoma of the Right Colon, *S. Clin. North America* **27**:361-372, 1947.

492. Threadgill, F. D.: Intestinal Lipoma Simulating Carcinoma of the Sigmoid Colon, *Am. J. Surg.* **73**:398-400, 1947.

493. McLaughlin, E. F.: Carcinoma of the Cecum in Association with Acute Appendicitis, *Am. J. Surg.* **72**:585-593, 1946.

494. Jarvis, J. L., and Cayer, D.: Cancer of the Cecum: A Review of the Clinical Features, *Am. J. Digest. Dis.* **14**:95-98, 1947.

495. Cole, W. H.: Carcinoma of the Colon, *Illinois M. J.* **91**:229-238, 1947.

496. Johnston, J. H., Jr.: Carcinoma of the Colon in Childhood and Adolescence, *Am. J. Surg.* **73**:703-712, 1947.

497. Fishback, H. R.: Carcinoma of the Transverse Colon in a Fifteen-Year-Old Boy: Case Report with Short Summary of the Literature, *Radiology* **48**:168-171, 1947.

Two carcinomas were found in 102 cases of diverticulosis.<sup>498</sup> Of 726 cases of cancer of the colon, multiple lesions occurred in 3 per cent.<sup>499</sup> The diagnosis depends on preoperative roentgen examinations and on careful exploration of the entire colon at the time of operation.

An encapsulated, semicystic, papillary mucous cystadenocarcinoma, weighing 8 pounds (3.6 Kg.) and measuring 50 cm. in diameter, was removed from the right groin of a 60 year old white man.<sup>500</sup> Though no involvement of the lumen of the colon was detected on palpation and grossly the tumor was entirely extraperitoneal, it was thought to have arisen from the cecum or the proximal portion of the ascending colon. Two instances of carcinoma of the colon simulating linitis plastica are reported.<sup>501</sup>

Five interesting cases of multiple carcinomas of the rectosigmoid are described.<sup>502</sup> Lahey<sup>503</sup> points out that although the clinical features of carcinoma of the colon and rectum may suggest an inoperable lesion exploratory operation should not be discouraged in view of the unpredictability of the rapidity of growth and metastatic involvement; this is particularly true of lesions of the right side of the colon, many of which appear inoperable clinically yet are found to be readily resectable.

*Sarcoma and Miscellaneous Lesions.*—A lymphosarcoma in a polyp on the posterior wall of the rectum was removed by fulguration; the patient was well five years later.<sup>504</sup>

Gotlieb<sup>505</sup> records an unusual case of intersigmoid hernia diagnosed roentgenologically. The diagnostic features consisted of considerable distention of proximal loops of small intestine, normal passage of barium apart from a temporary stop at the sigmoid at the level of the herniation, obvious extrinsic pressure resembling a poorly defined filling defect in the sigmoid but varying with change in the position of the patient. normal

498. Oren, B. G.: Diverticulosis Coli with Coexisting Carcinoma of the Rectosigmoid, *South. M. J.* **40**:304-308, 1947.

499. Mider, G. B.: Multiple Invasive Carcinomas of the Large Intestine, *Surgery* **20**:744-748, 1946.

500. Castro, A. F.; Barga, J. A.; Clagett, O. T., and Dockerty, M. B.: Cystic Tumor of Right Groin: A Complication of Carcinoma of the Colon, *Gastroenterology* **8**:95-100, 1947.

501. Karstens, H. C., and Barga, J. A.: Carcinoma of the Colon Simulating Linitis Plastica: Report of Two Cases, *Proc. Staff Meet., Mayo Clin.* **22**:231-259, 1947.

502. D'Allaines, F., Bensaude, A., and Motoños, G.: Contribution à l'étude des cancers multiples primitives du rectum, *Arch. d. mal. l'app. digestif.* **35**:392-403, 1946.

503. Lahey, F. H.: Prognosis of Patients with Carcinoma of the Colon, Rectosigmoid and Rectum, *S. Clin. North America* **27**:670-674, 1947.

504. Harris, F. I., and Feigen, G. M.: Lymphosarcoma of the Rectum: Five Year Cure Following Local Removal, *Am. J. Surg.* **72**:277-279, 1946.

505. Gotlieb, G. G.: A Case of Intersigmoid Hernia with Illustrations of X-Ray Appearances, *Brit. J. Radiol.* **19**:429-431, 1946.

emptying of the colon by evacuation, localized tenderness on palpation and an isolated gas bubble in the arrested coil of small intestine, seen more distinctly in the erect position and separable from the sigmoid by manual pressure.

Cattell and Colcock<sup>506</sup> report seven unusual lesions of the large intestine consisting of cystic disease of the bowel, lymphosarcoma of the cecum, nonspecific cicatrizing regional ulcerative colitis, endometriosis of the colon, leiomyosarcoma, lymphogranuloma venereum and basal cell carcinoma of the rectum.

*Colostomy.*—Jones and Kehm<sup>507</sup> describe the management of the patient with a permanent colostomy opening and direct attention to the various complications which may ensue, including difficulty in irrigation, prolapse or constriction of the opening, hernia, bleeding and diarrhea.

#### DISEASES OF THE ANUS AND RECTUM

*Congenital Malformations.*—Rosenblatt and May<sup>508</sup> report 20 cases of malformation. A duplication of the rectum which assumed the characteristics both of a cyst and of a diverticulum was treated successfully by marsupialization.<sup>509</sup>

*Pruritus Ani.*—Swinton<sup>510</sup> points out that the scratch-itch syndrome is a basic factor in the background of a large number of patients with an intractable anal pruritus. In intractable cases the initial precipitating factor may have disappeared or have become so altered that it is no longer significant. The possible precipitating causes are numerous and include physiologic, infective, allergic, psychogenic and mechanical factors. The physical examination should include an anoscopic and proctoscopic examination. Adequate rest, relaxation and relief from tension are required. When first seen, patients should be given a brief but intelligent discussion of the subject and routinely advised to wash themselves often with cotton moistened in warm water; toilet tissue and soap should be eliminated. The ensuing dryness and cleanliness and the avoidance of trauma will definitely control most of the mild forms. Surgical intervention should be limited to removal of sources of infection and the correction of obvious local disease. Injections of alcohol relieve the scratch-itch syndrome but should be reserved for the severe cases. The importance of psychogenic

506. Cattell, R. B., and Colcock, B. P.: Unusual Lesions of the Large Intestine, *S. Clin. North America* **27**:651-658, 1947.

507. Jones, T. E., and Kehm, R. W.: Management of the Permanent Colostomy, *Cleveland Clin. Quart.* **13**:198-202, 1946.

508. Rosenblatt, M. S., and May, A.: Malformation of the Anus and Rectum, *Surg. Gynec. & Obst.* **83**:499-506, 1946.

509. Cogswell, H. D., and Thompson, H. C., Jr.: Duplication of the Rectum, *Am. J. Dis. Child.* **73**:167-174, (Feb.) 1947.

510. Swinton, N. W.: Pruritus Ani, *New England J. Med.* **236**:169-172, 1947.

mechanisms should never be overlooked. Gardner<sup>511</sup> devised a surgical treatment consisting of Gabriel's hemorrhoidectomy modified by the removal of a much larger portion of the skin around the anus; the results are reported as excellent for all 35 patients so treated. The reviewers are of the opinion that careful adherence to Swinton's program and also to that prescribed by Shapiro and Rothman (*Gastroenterology* 5: 155-168, 1945) will almost completely eliminate any need for Gardner's operation.

*Miscellaneous Conditions.*—Granet<sup>512</sup> considers coccygodynia to be due in most cases to reflex spasm of the coccygeal muscles; tender bursas over the levator ani may be partially responsible for the pain. Anorectal abscesses are reviewed by Wenzel.<sup>513</sup> Bacon and his associates,<sup>514</sup> in a comprehensive discussion of diseases of the rectum, conclude that strictures of all types are best treated by perineal excision preceded by a permanent colostomy. Mere anal stenosis is successfully corrected by attaching mobilized mucous membrane to the marginal wound.

A large enterogenous cyst arising from the rectum produced a non-tender 12 by 11 cm. cystic mass containing 600 cc. of thick tenacious material; the intestinal wall had undergone fibrosis, hyalinization, deposition of calcium and pressure atrophy of the epithelial lining.<sup>515</sup>

Twenty-five cases of carcinoma of the anus treated by irradiation, with adequate follow-up, are reviewed by Meland,<sup>516</sup> with the conclusion that irradiation offers reasonable expectation of complete recovery, with added hope of sphincter control.

#### MISCELLANEOUS GASTROINTESTINAL SUBJECTS

*Preoperative and Postoperative Care.*—Among a series of 250 patients treated preoperatively and postoperatively with either "sulfasuxidine" (succinylsulfathiazole), "sulfathaladine" (phthalylsulfathiazole) or both there were no instances of demonstrable or fatal peritonitis, fecal fistulas, or wound disruptions.<sup>517</sup> The effectiveness of these drugs is at-

511. Gardner, C. M.: Pruritus Ani, *Canad. M. A. J.* **55**:259-262, 1946.

512. Granet, E.: Proctalgias and Allied Non-Inflammatory Perianal Dyscrasias: Coccygodynia, Proctalgia Fugax, Neurogenic Pruritus Ani, *Am. J. Digest. Dis.* **13**:330-333, 1946.

513. Wenzel, J. F.: Anorectal Abscesses, *Am. Surg.* **72**:517-525, 1946.

514. Bacon, H. E.; Fleming, J. P.; Pedlow, L. L.; Smith, C. H.; Holoman, M. B., and Rowe, R. J.: The Diagnosis and Treatment of Diseases of the Anorectum, *Am. J. Med.* **1**:257-267, 1946.

515. Custer, B. S.; Kellner, A., and Escue, H. M.: Enterogenous Cysts: Report of Case Involving the Rectum, *Ann. Surg.* **124**:508-518, 1946.

516. Meland, O. N.: Carcinoma of the Anus, *Am. J. Roentgenol.* **57**:199-204, 1947.

517. Poth, E. J.: Sulfasuxidine and Sulfathalidine in Surgery of the Colon, *South. M. J.* **40**:369-375, 1947.



tributed to their antibacterial action, to the mechanical removal of gas and feces, to the reduction of distention and to the earlier administration of a high protein diet.

Amino acids administered orally or parenterally may be used as a protein substitute although palatability in the oral preparations is yet to be obtained.<sup>518</sup> Caution is recommended in the rapid intravenous administration. Plasma is expensive and lacks two essential amino acids.

*Peritoneum.*—Ivanissevich and Defazio<sup>519</sup> report a rare case of gelatinous disease of the peritoneum.

*Retroperitoneal Tumors.*—Cattell and Warren<sup>520</sup> describe five retroperitoneal lipomas. The surgical removal of these tumors is attended by a 20 to 25 per cent mortality, death occurring from hemorrhage and shock due to their enormous size and their close relation to the great vessels and other retroperitoneal viscera.

Among ninety-five retroperitoneal tumors, the most frequent types were sarcoma (14), fibrosarcoma (18) and undifferentiated neoplasms (23).<sup>521</sup> Metastasis and local recurrences occurred in about 30 per cent of the cases. Adams<sup>522</sup> reports four interesting mesenteric tumors.

*Abscess.*—Occasionally, gas formation is the most significant roentgenologic sign of an abdominal abscess, and it often aids in the differentiation from tumor and hematoma.<sup>523</sup> Gas formation in abdominal abscesses does not necessarily indicate the presence of an infection due to *Clostridium welchii* and related bacteria, since it may be caused by such organisms as aerobic streptococci and *E. coli*.

*Trauma.*—Crohn<sup>524</sup> discusses this important subject and presents illustrative cases.

*Military Gastroenterology.*—According to Chamberlin,<sup>525</sup> functional disorders, epidemic diarrhea and peptic ulcer caused the greatest numbers

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518. Remington, J. H.; Barga, J. A., and Lundy, J. S.: Amino Acid Alimentation in Gastro-Intestinal Diseases, *Gastroenterology* 7:442-449, 1946.

519. Ivanissevich, O., and Defazio, F.: *Maladie gelatineuse du péritoine*, *Semana méd.* 53:554-566, 1946.

520. Cattell, R. B., and Warren, K. W.: Retroperitoneal Lipoma, *S. Clin. North America* 27:659-665, 1947.

521. Donnelly, B. A.: Primary Retroperitoneal Tumors: A Report of Ninety-Five Cases and a Review of the Literature, *Surg., Gynec. & Obst.* 83:705-777, 1946.

522. Adams, H. D.: Mesenteric Tumors, *S. Clin. North America* 27:666-669, 1947.

523. Weens, H. S.: Gas Formation in Abdominal Abscesses: A Roentgen Study, *Radiology* 47:107-115, 1946.

524. Crohn, B. B.: The Relationship of Trauma to Diseases of the Gastro-Intestinal Tract, *Gastroenterology* 8:735-742, 1947.

525. Chamberlin, D. T.: Military Gastro-Enterology: The Summing Up, *Gastroenterology* 7:162-167, 1946.

of gastrointestinal disabilities in the service. The incidence of peptic ulcer among combat troops was not higher than that in civilian life. Patients with functional digestive disorders constituted about one third of all those admitted to general hospitals for symptoms related to the digestive tract.

*Macroglossia.*—Baber<sup>526</sup> describes an instance of amyloid macroglossia, the fourth to be reported in England. As in previous cases, the deposits were located chiefly in the tongue, skeletal muscles and heart.

*Abdominal Pain.*—The various theories and controversial issues concerning the mechanisms of abdominal pain are reviewed by Schutz.<sup>527</sup> Stickney,<sup>528</sup> in a discussion of acute abdominal pain, points out that the differentiation of visceral and root pain by paravertebral block or local infiltration with anesthetic agents is not reliable since such procedures interrupt the visceroparietal reflex and, therefore, may abolish the pain of visceral disease as well as that of the nerve roots.

Moore<sup>529</sup> defines abdominal epilepsy as a disorder characterized by bouts of paroxysmal abdominal pain due to hypermotility of the bowel, provoked by abnormal nervous impulses originating presumably in the premotor and postmotor cortex or in the diencephalon. Various organic conditions may serve as trigger mechanisms for the epileptic discharge. In general, such mechanisms involve biophysiochemical disturbances such as hypoglycemia and cerebral anoxia.

*Allergy.*—Gastrointestinal allergy, according to Chobot,<sup>530</sup> is most frequently seen in children up to the age of 5. It is encountered in the adult most often in cases of urticaria and angioedema. There are two mechanisms of allergic reaction. In the immediate type symptoms follow ingestion of food within fifteen minutes to an hour. There are positive cutaneous reactions and skin-sensitizing antibodies are present in the blood. In the delayed reaction, symptoms follow ingestion of food after one to seventy-two hours. There are no positive cutaneous reactions and no circulating skin-sensitizing antibodies in the blood. Ninety-eight per cent of the food allergies in children undergo spontaneous involution. Chobot points out that too often vague symptoms of indigestion are

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526. Baber, M. D.: Amyloid Macroglossia, *Lancet* 1:210-211, 1947.

527. Schutz, P. J.: The Causes and Mechanisms of Abdominal Pain, *Am. J. Digest. Dis.* 13:299-307, 1946.

528. Stickney, J. M.: Medical Problems in Cases of Acute Abdominal Pain, *M. Clin. North America* 30:913-917, 1947.

529. Moore, M. T.: Symptomatic Abdominal Epilepsy, *Am. J. Surg.* 72:883-899, 1946.

530. Chobot, R.: Gastro-Intestinal Allergy, *Am. Pract.* 1:315-316, 1947.

promptly labeled as evidence of allergy without further evidence, a statement with which the reviewers are in complete accord.

*Meningococcic Meningitis with Hemorrhage.*—Gray and Talisman<sup>531</sup> report fulminating meningococcic meningitis accompanied with a massive gastrointestinal hemorrhage; the patient recovered, and the exact source of the bleeding was not determined.

*Abdominal Apoplexy.*—Spontaneous rupture of a splenic arterial vessel, or so-called abdominal apoplexy, is reported and the records of 35 cases analyzed.<sup>532</sup>

Hunt and Weller<sup>533</sup> describe an instance of rupture of an abdominal aortic aneurysm into the gastrointestinal tract and briefly review 40 similar cases previously reported. The third portion of the duodenum is most frequently involved. Important clinical criteria are an abdominal tumor, almost always pulsating, in 60 per cent of cases, roentgen signs in 75 per cent and pain in the abdominal or lumbar region. Hematemesis is usually terminal.

*Actinomycosis.*—The clinical manifestations and the treatment of abdominal actinomycosis are reviewed on the basis of 5 cases.<sup>534</sup> The appendix is the site of origin in most instances. The portal of entry is thought to be the alimentary tract. Peritonitis occurs only if there is perforation of the intestine. Prolonged chemotherapy (sulfadiazine) combined with adequate surgical care is presented as the treatment of choice.

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531. Gray, I., and Talisman, M. R.: Massive Gastrointestinal Hemorrhage in Fulminating Meningococcus Meningitis (Waterhouse-Freiderichsen Syndrome) with Recovery, New York State J. Med. 47:1389-1391, 1947.

532. Tanna, J. F.: Abdominal Apoplexy, Am. J. Surg. 73:132-136, 1947.

533. Hunt, H. H., and Weller, C.: The Syndrome of Abdominal Aortic Aneurysm Rupturing into the Gastrointestinal Tract, Am. Heart J. 32:571-578, 1946.

534. Farris, E. M., and Douglas, R. V.: Abdominal Actinomycosis, Arch. Surg. 54:434-444 (May) 1947.

## Book Reviews

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**Experimental Catatonia: A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology.** By Herman Holland de Jong, M.D. Price, \$4. Pp. 225. Baltimore: Williams & Wilkins Company, 1945.

The experimental production of catatonia in animals by the use of bulbocapnine was first described by the author and Baruk in 1930. The present book represents an extension and an expansion of that significant research. A variety of substances are now known to produce catatonic signs. The first part of this book consists of detailed and extensive protocols of numerous experimental studies. Catatonia was induced by means of drugs, asphyxiation, centrifugation, surgical occlusion of the carotid arteries, audiogenic stimulation and other methods.

The implications for human pathology, with particular reference to catatonic schizophrenia, are presented in the second part of the book.

Dr. de Jong concludes that experimental catatonia is analogous to epileptiform seizures in that both conditions represent nonlocalized diffuse reactions of the central nervous system. He offers the suggestion that cellular asphyxiation may be responsible for the onset of catatonic signs.

He believes that schizophrenia is primarily an "organic" disease, the mental symptoms being secondary phenomena. He cautiously suggests that there may be a toxic etiologic agent in this disease since "only alterations of the function of the liver and the intestine proved capable of producing experimental catatonia," lesions of the other organs having no such effect. Abnormal reactions to liver function tests on catatonic schizophrenics suggested the possibility of primary hepatic damage resulting in the formation of a toxic protein metabolite which may produce cellular anoxia in the nervous tissues and resultant catatonic signs.

This book is skillfully written and authoritative, and it represents stimulating research by an internationally known scientists. It should be of great interest to physicians and to research workers concerned with the physiologic approach to the baffling problem of the etiology of schizophrenia.

**Nogle respirationsfysiologiske undersøgelser ved lungetuberkulose: Thoracoplastikkens indflydelse paa lungevolumen den alveolaere ventilation belyst ved fractioneret alveoleluftanalyse.** By Ulf Gad. Pp. 159. Copenhagen: G. E. C. Gads Forlag, 1941.

This monograph, written in Danish with an English summary, presents studies in preoperative and postoperative lung volumes and composition of alveolar air on patients with pulmonary tuberculosis subjected to thoracoplasty. The first of three chapters deals with the effect of thoracoplasty on lung volume in 51 subjects. Vital capacity was determined spirometrically and compared with results derived from West's formula. Residual air was determined by the hydrogen dilution method. Patients with tuberculosis usually had lowered total capacities and often relatively high residual fractions preoperatively. Postoperatively, the

vital capacity was further reduced, but in 24 per cent the residual air was increased. He found patients to be dyspneic on exertion if vital capacity was less than half of the calculated normal amount. Incidentally, the use of roentgenologic planimetry in estimation of lung volume was found unreliable because of wide individual variation.

The second chapter gives the extremely variable results of testing 78 patients for "mixing capacity" after the manner of Lundsgaard and Schierbeck.

The last chapter reports fractional gas analyses on expired and alveolar air both preoperatively and postoperatively with the use of Sonne and Nielsen's apparatus after single inspirations of pure hydrogen. Hydrogen content on expiration decreased more rapidly than normally, and the rate of decrease varied with the severity of the pulmonary tuberculosis. On the other hand, since oxygen values in expired air were more nearly normal in these subjects, the author assumes that blood flow must have decreased in the poorly ventilated parts of the lungs (62 patients).

The author concludes that dyspnea in his patients was due to changed lung volumes and to disturbed alveolar ventilation and that dyspnea might have been worse but for compensating alterations in alveolar blood perfusion. Ingenious charts are included.

Since this work was published, direct measurements of ventilation capacity have shown that vital capacity taken alone can be no criterion of ventilation. Gray, Cournand and others have further clarified the subject of pulmonary function, developing and applying clinically useful tests in studies made on normal and on diseased subjects.

This study is one of the first to compare strictly preoperative and postoperative testing in large series of cases of thoracic disease requiring surgical treatment; it deserves the attention of those who are interested in respiratory physiology and thoracic diseases.

**The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities.**

By Philip Lewin, M.D. Third edition. Price \$11 (buckram). Pp. 847, with 389 illustrations. Philadelphia: Lea & Febiger, 1947.

Whether it is logical to assemble in one massive book everything to be known about the foot is an interesting question for discussion. For example, should arthritis of the foot be discussed in a book on arthritis or in a book on the foot? Do the circulatory disturbances in the foot belong under the same covers with bunions or are the latter best dealt with in an orthopedic treatise? Be this as it may, Dr. Lewin's book is now in its third edition, so that there is evidently a place for topographic medicine of this sort. The volume is a handsome one, well and profusely illustrated, and there is a lengthy bibliography. The reviewer is glad to have the book on his shelves.

**Maladies et syndromes rares ou peu connus.** By A. Aimes, M.D. Pp. 208, with 26 illustrations. Paris: Masson & Cie, 1946.

As the title of this monograph indicates, most of the rare medical syndromes are discussed. The syndrome is defined and the characteristics summarized. It is an extremely useful book.

## PHEOCHROMOCYTOMA WITH SYMPTOMS OF EPINEPHRINE SHOCK

Report of a Case

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AND

ROBERT G. ANGLE, M. D.  
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The clinical syndrome associated with pheochromocytoma of the adrenal gland is well recognized and the modern literature contains records of cases in which the condition was diagnosed and surgically treated and the patient cured. However, the classic symptoms are not invariably present, and occasionally this tumor is accidentally discovered at autopsy apparently unassociated with any symptom pattern or with the cause of death. In some instances medical aid is not sought until the terminal fulminating episode, during which the patient may present a variety of symptoms which tax the ingenuity of the most astute diagnostician. Such was the nature of the case to be presented.

### REPORT OF A CASE

A 32 year old soldier, assigned to duty in India, became suddenly ill on Aug. 29, 1945, at 9 a.m., with palpitation, dyspnea, epigastric pain, nausea and vomiting. The vomitus was watery in consistency, and, according to the patient, blood tinged. The soldier remained in his quarters, where he was first examined by a medical officer. At that time the only essential finding was a tachycardia of 120, with a regular pulse rate of fair volume. He did not appear acutely ill and so was permitted to remain in quarters. However, several hours later his condition became worse. He appeared pale and was drenched with perspiration. The epigastric pain persisted but was somewhat alleviated by changing positions. The temperature was 100.2 F., the pulse rate 120, the respirations 44 and the blood pressure 140 systolic and 120 diastolic. Widely dilated pupils were observed which reacted sluggishly to light. There were moist rales throughout the lower lobes of both lungs. The heart rate was rapid and regular, but no abnormal sounds were elicited. A mottled cyanosis of the extremities was conspicuous. Abdominal examination revealed nothing significant.

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From the Twentieth General Hospital, India.

Dr. Ferraro is a pathologist at St. Francis Hospital, Poughkeepsie, N. Y.

On his admission to the hospital, 0.032 Gm. of morphine sulfate was administered hypodermically and external heat applied to the body. Oxygen therapy was instituted continuously. He appeared to improve slightly under this regimen, but this change was temporary. By 7 p.m. that day the temperature reached 104.2 F. and the pulse rate, barely perceptible, 156. In view of this unexplained temperature, 50,000 units of penicillin was administered. However, alarming symptoms soon appeared. The cutaneous surfaces became cold, especially over the extremities, and profuse perspiration continued. Later, shallow respirations, progressive cyanosis, a temperature of 106.4 F. and coma developed. Death occurred at 11:40 p.m., fourteen hours after the onset of his symptoms.

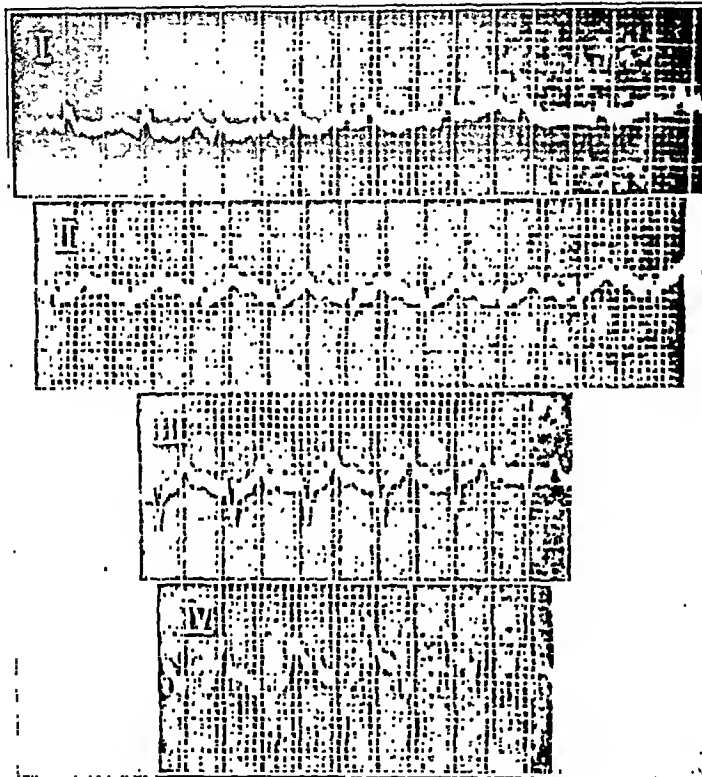


Fig. 1.—Electrocardiogram showing left axis deviation and sinus tachycardia. (Seventh Medical Museum and Arts Department negative no. G-4592.)

The laboratory data were as follows: The red blood cell count was 6,300,000 and the white blood cell count 20,000, with 82 per cent polymorphonuclear cells, 8 per cent lymphocytes and 10 per cent monocytes. The electrocardiograph (fig. 1) showed a rate of 122 and a QRS wave of 0.08 seconds.

The QRS wave in lead I was splintered, in lead II diphasic and in lead III inverted; the T wave was upright. This was interpreted as indicating (1) left axis deviation and (2) sinus tachycardia.

Subsequent to the death of the patient, additional significant history was obtained from a friend, who informed us that the patient had experienced several attacks of palpitation while on board ship en route to India. These attacks lasted several hours and subsided spontaneously. There is no available information regarding either the physical findings or the therapy instituted on these occasions.

*Observations at Necropsy.*—The essential findings at necropsy are summarized as follows:

**Heart:** The heart weighed 400 Gm. The first inch of the left anterior descending artery revealed a prominent eccentric atheromatous deposit producing a crescentic narrowing of the lumen.

**Left Adrenal Gland:** A large encapsulated tumor conspicuously occupied the position of the left adrenal gland and measured 7 by 5 by 4 cm. It weighed 70 Gm. At the superolateral border a compressed and displaced portion of the adrenal gland was noted merging imperceptibly with the mass. The latter was reddish brown,

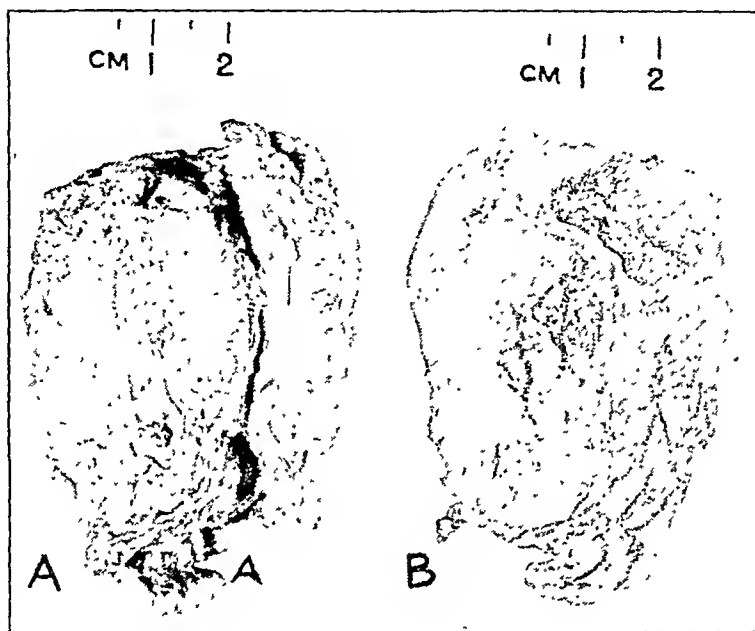


Fig. 2.—A, surface view of the tumor. Compressed portion of adrenal at A. B, cut section of tumor revealing pseudocystic cavities. (Seventh Medical Museum and Arts Department negative nos. A-451081-1 and A-451081-2.)

tensely cystic and completely encapsulated. On section, about 10 cc. of dark hemorrhagic fluid was released under pressure. Two irregular pseudocystic cavities occupied the central region, surrounded by a rim of soft golden yellow and brownish tissue.

**Right Adrenal Gland:** This was normal on gross examination.

**Other Organs:** The rest of the organs did not show any significant changes.

**Microscopic Examination:** Section of the tumor revealed a diffuse proliferation of normal-appearing chromaffin cells surrounded by a delicate fibrous stroma in which occasional dilated capillaries were noted. The diagnosis was pheochromocytoma.

#### COMMENT

The pathogenesis of "epinephrine shock" in pheochromocytoma is not understood in its entirety although several important experimental, clinical and pathologic observations have helped to clarify this condition.



Freeman, Freedman and Miller<sup>1</sup> succeeded in producing shock by the continuous injection of epinephrine in unanesthetized dogs. They described symptoms of moderate hyperpnea and restlessness shortly after injection, with vomiting as a frequent occurrence. At the end of one

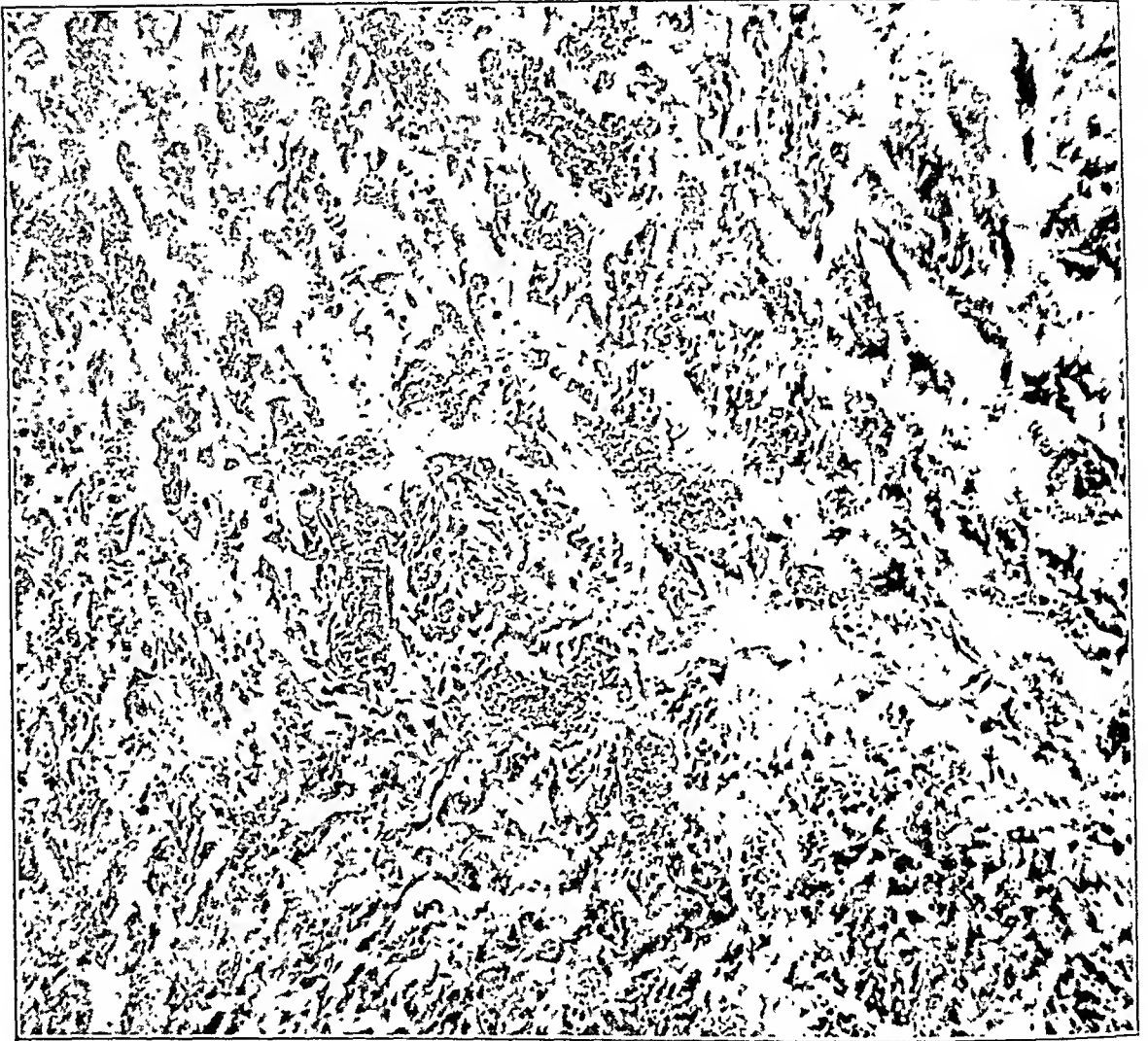


Fig. 3.—Masses of chromaffin cells surrounded by an irregular fibrous stroma; low power magnification. (U. S. Army Medical Museum negative no. 90714.)

hour, clinical symptoms of shock were marked. Other symptoms noted were pallor, cyanosis, coldness of the ears and extremities, thready pulse, rapidly rising temperature, excessive hypertension later subsiding and decreasing plasma volume. The latter was thought to be initiated by anoxia of the peripheral capillaries following prolonged vasoconstriction, eventuating in a loss of fluid into the tissues. These authors emphasized the altered status of the plasma proteins as a mechanism in the

1. Freeman, N. E.; Freedman, H., and Miller, C. C.: Production of Shock by Prolonged Continuous Injection of Adrenalin in Unanesthetized Dogs, *Am. J. Physiol.* 131:545-553 (Jan.) 1941.

production of shock and were able to relieve this condition in several dogs by the use of blood transfusions and the intravenous injection of hypertonic solution of dextrose.

From the clinical standpoint, it is generally agreed that "epinephrine crises" are associated with a characteristic group of symptoms among which may be mentioned hypertension, coldness of the extremities, with blanching or mottling of the skin, diaphoresis, accelerated

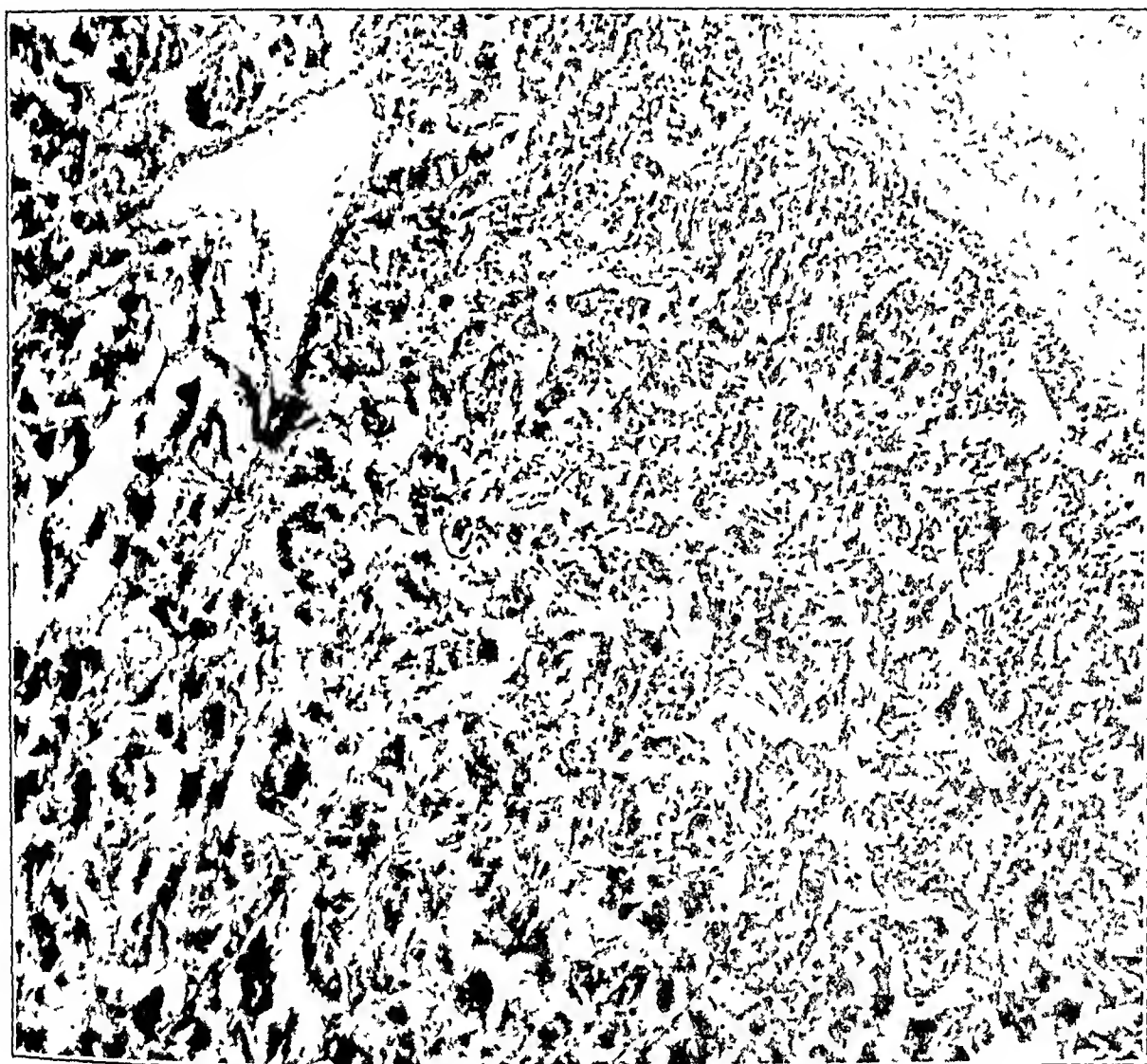


Fig. 4.—Typical pattern of chromaffin cells; high power magnification. (U. S. Army Medical Museum negative no. 90713.)

heart rate, dyspnea and varying degrees of shock. These symptoms have been found in a sufficiently large number of proved cases to warrant the assumption of a direct relationship with the pheochromocytoma.

The demonstration of a pressor substance during a crisis has not met with universal success. This is readily understood when the relatively small amount of the offending substance, presumably epinephrine, in the circulating blood is appreciated, as well as the difficulty of its

identification. However, in 1937, Beer, King and Prinzmetal<sup>2</sup> reported a case of pheochromocytoma and demonstrated the presence of a pressor substance in the blood. After the surgical removal of this tumor, no similar substance could be recovered from the plasma.

Pathologic studies of surgical specimens and of specimens at autopsy have established certain fundamental facts. First, the tumor is composed of hyperplastic chromaffin cells duplicating the appearance of the normal adrenal medulla. A few malignant tumors have been recorded, but these are rare. Secondly, chemical tests applied to the tumors at the time of removal have indicated the presence of epinephrine in increased amounts. Kalk<sup>3</sup> reported the findings of 375 to 500 mg. of epinephrine in a neoplasm of this type as compared to a normal of approximately 4 mg. Belt and Powell<sup>4</sup> reported a case in which the tumor yielded 2 Gm. of epinephrine per hundred grams of tissue.

Thus it appears that the syndrome during an "epinephrine crisis" results from an abnormal release of epinephrine into the general circulation. The initiating factors capable of inducing this state may vary, although mechanical pressure over the site of the tumor and physiologic stimuli such as fear, anger or excitement are frequent offenders. In view of the paroxysmal nature of these attacks, it must be assumed that during the interim state of well-being, the release mechanism is held in abeyance.

#### SUMMARY

1. A case of pheochromocytoma which terminated fatally after "epinephrine shock" is reported.
2. Experimental, clinical and pathologic evidence is submitted for the explanation of this syndrome.

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Gen. Isadore Ravdin and Col. Francis Wood granted us permission to report this case.

2. Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, *Ann. Surg.* **106**:85-91 (July) 1937.

3. Kalk, H.: Paroxysmale Hypertension: Blutdruckkrisen und Tumor des Nebennierennorkes, *Klin. Wchnschr.* **13**:613-617 (April 28) 1934. .

4. Belt, A. E., and Powell, T. O.: Clinical Manifestations of Chromaffin Cell Tumors Arising from Suprarenal Medulla: Suprarenal Sympathetic Syndrome, *Surg., Gynec. & Obst.* **59**:9-24 (July) 1934.

# TROPICAL ANHIDROTIC ASTHENIA

## Its Definition and Relationship to Other Heat Disorders

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If it be a turbulent, rough, cloudy, stormy weather, men are sad, lumpish, and much dejected, angry, waspish, dull and melancholy.—*Robert Burton*.<sup>1</sup>

Why does long residence tend to annul adjustment to the tropics? The explanation is complex and involves many functions of both mind and body.<sup>2</sup> Inasmuch as all authorities agree that man needs efficient sweat glands, it is odd that disorders of sweating have failed to gain full notice in relation to the vicious results of heat. Despite intense study of the normal activity of the sweat glands, it has hitherto been true that little was known of the ill effects of their incompetence on tropical health. Such information as was available dealt chiefly with congenital deficiencies of the glands. But the congenital disease is a medical curiosity, and its study solves little of the larger problem of acquired intolerance to heat.

However, as a result of the recent war several reports have appeared which describe a temporary failure of sweating (anhidrosis)<sup>3</sup> and the general disability which results therefrom. It would seem that there exists a newly recognized syndrome of heat exhaustion associated with and probably caused by an anhidrosis of a large part of the body's surface. The disease, which constitutes a specific form of tropical deterioration, is more subtle than the classic heat disorders and easily eludes detection.

It has been reported from several parts of the world by three different teams. Wolkin, Goodman and Kelley,<sup>4</sup> working in the Amer-

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1. Shilleto, A. R.: *The Anatomy of Melancholy*, London, George Bell and Sons, 1893, pt. 1, sect. 2, memb. 2, subsect. 5.

2. Kark, R. M., and others: *Tropical Deterioration and Nutrition: Clinical and Biochemical Observations on Troops, Medicine* **26**:1 (Feb.) 1947.

3. This word, meaning decrease or failure of sweating, is also spelt "anidrosis" or "anhydrosis." Although somewhat cumbersome, "anhidrosis" appears to have the widest usage.

4. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: *Failure of the Sweat Mechanism in the Desert: Thermogenic Anhidrosis, J.A.M.A.* **124**:478 (Feb. 19) 1944.

ican desert area, called it "thermogenic anhidrosis." Ladell, Waterlow and Hudson<sup>5</sup> reported it from Southern Iraq under the name "heat exhaustion, type II." Allen and O'Brien<sup>6</sup> observed it in the South West Pacific area and gave it the name "tropical anhidrotic asthenia." Recently,<sup>7</sup> I have given a further account of anhidrotic asthenia, chiefly from the points of view of etiology, histology and treatment. The present paper, which is based on the one just mentioned, includes some more clinical features and, in particular, integrates my own observations with those of others. Critical correlation may be useful as there is often difficulty in deciding which elements truly belong to a newly described entity and which do not.

Stuart D. Allen<sup>6</sup> was the first to recognize the syndrome in soldiers who were stationed in the Northern Territory of Australia. Six patients admitted to hospital under his care early in 1943 gave a similar history of exhaustion, headache and dyspnea when working in the heat. Most had suffered from miliaria rubra (prickly heat) a short time before the onset of general symptoms. Allen noted the dry skin and the goose-flesh-like rash which these subjects characteristically show on exertion.

The present account is based on 38 typical severe cases observed over three wet seasons and includes, by permission, those which Allen originally found and demonstrated. This total is only a small, undetermined fraction of the cases which actually occurred amongst Australian troops in the South West Pacific. Indeed, because of service memorandum,<sup>8</sup> most Australian medical officers in the area were able to recognize the disease, if only in a mild form, among troops under their own care. Besides those in the Northern Territory of Australia, I have seen patients at Merauke (Dutch New Guinea)<sup>9</sup> and Morotai (Moluccas) and others evacuated from Dutch Borneo. Novy and Ramsey<sup>10</sup> encountered 2 cases in New Guinea and Ginsberg,<sup>11</sup> 3 at Cape

5. Ladell, W. S. S.; Waterlow, J. C., and Hudson, M. F.: *Desert Climate: Physiological and Clinical Observations*, *Lancet* 2:491 (Oct. 14); 527 (Oct. 21) 1944.

6. Allen, S. D., and O'Brien, J. P.: (a) *Tropical Anhidrotic Asthenia*, *M. J. Australia* 2:335 (Sept. 23) 1944; (b) abstracted, *Bull. War Med.* 5:486 (April) 1945.

7. O'Brien, J. P.: *A Study of Miliaria Rubra, Tropical Anidrosis and Anhidrotic Asthenia*, *Brit. J. Dermat.* 59:125 (April-May) 1947.

8. O'Brien, J. P.: *Dysfunction of the Skin in the Tropics*, a memorandum prepared in 1944 for the Director-General and distributed officially within the Australian Army Medical Corps.

9. The average weather conditions in the wet season at Merauke, where most of the present work was done, were as follows: The maximum temperature (afternoon) was 90 F. and the relative humidity 65 per cent. The minimum temperature (early morning) was 65 F. and the relative humidity 100 per cent.

10. Novy, F. G., Jr., and Ramsey, J. H.: *Failure of the Sweat Mechanism in the Desert*, *J.A.M.A.* 125:738 (July 8) 1944.

11. Ginsberg, M. W.: Personal communication to the author.

York (Australia). More recently, Sulzberger, Zimmerman and Emerson<sup>12</sup> have found and investigated the disease in the United States Navy on Guam. It is more prevalent than superficial observation would suggest. By means of regular inspections, Kendall<sup>13</sup> detected 28 cases among 440 members of a battalion in Merauke during ten months of 1944—an incidence of 6 per cent. All the affected men were not sick enough to need treatment in hospital, but at best they were unable to continue full duty. There seems little doubt that the disease can occur wherever severe miliaria is found. Mild cases and cases in which the subjects show only the cutaneous signs (simple tropical anhidrosis)<sup>7</sup> are frequently observed.

The onset of the disease is rather insidious, although it may be acute in those who have had a particularly intense, diffuse attack of miliaria. When the speed of onset is being estimated, it should be kept in mind that the disease can be present but not manifest until such time as the subject undertakes physical exertion. Typically, the patient notices, over a period of a week or two, that exercise in the heat of the day, especially in bright sunshine, produces an unusual degree of exhaustion and sensation of heat as well as throbbing frontal headache, giddiness, dyspnea and palpitation; if the exertion is continued, transient dimness of vision may occur. In other words, the subject shows an excessive fatigue response to exercise. Fainting is not a feature unless the earlier warning symptoms have been unheeded. True coma does not occur. When the disease is severe, exercise, such as wood chopping, is impossible for more than a few minutes.

Subjectively, the skin is hot as though burning and has a feeling of fulness or tenseness. Pruritus may be present but only, as a rule, when some miliarial lesions still persist from the antecedent attack. In practically every instance the patient states that the pruritus of miliaria has improved by the time general symptoms begin, and in some cases no sensations of the skin are felt during the phase of general symptoms.

The patient sometimes notices that the trunk and limbs are dry. More often he comments on the profuse sweating (hyperhidrosis) which regularly appears from the forehead and face during exercise. Sweat runs into the eyes from the forehead and onto the chest from the neck and chin. This heavy sweating from the exposed parts of the head often deludes both subject and observer into believing that sweating generally is not diminished.

On examination, the patients are exhausted, frequently to the extent that tremor, and incipient fainting are observed. The respirations are

12. Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K.: Tropical Anhidrotic Asthenia (Thermogenic Anhidrosis) and Its Relationship to Prickly Heat, *J. Invest. Dermat.* 7:153 (Aug.) 1946.

13. Kendall, B.: Personal communication to the author.

increased in depth, and the rate is up to 50 excursions per minute, the pulse is accelerated to an average of 160 beats per minute and the oral temperature is raised to an average of 100 F. (37.8 C.). The highest oral temperature recorded in the present series was 102.6 F. (38.9 C.).

The cutaneous changes are characteristic, providing they are looked for immediately after exercise; they are less striking at other times. Most or all of the covered parts are partly or completely devoid of sweat and studded with innumerable deep, matt white vesicles,<sup>14</sup> each 1 mm. or less across, the general effect being like that of goose flesh. However, the vesicles do not surround hairs as do the elevations of true goose flesh. The intervening skin is not red. Superficial miliarial vesicles with red areoli and red miliarial papules may still be present, either in isolated groups or else scattered thinly among the more numerous typical lesions. To touch, the skin is hot, thickened and particularly dry.

The palms and soles are never affected by the rash and in most instances sweat normally but not profusely. The axillas and the folds of the groin may or may not be dry. On the legs, ichthyoid changes are more common than a typical rash. A fairly constant feature is a moderate, persistent enlargement of the axillary and inguinal lymph glands. The relative or complete dryness of the covered parts and the associated rash are regarded as pathognomonic when taken in conjunction with the asthenic symptoms and signs.

When the patient lies in a cool place the various manifestations pass off in from half an hour to three hours. If it is extremely hot, the rash may persist but in a less obvious form. Should further exercise be undertaken, the clinical picture soon reappears exactly as before.

Apart from the discomforts of physical exercise, the patient may feel fairly comfortable and be able to carry out light duties. However, some continuous lack of appetite and in the day's heat some listlessness and headache are often felt. Frequency of micturition and polyuria are occasionally noticed, though more usually urinary symptoms have largely passed off by the time the patient reports ill.

The duration of the disease when untreated is variable, but as a rule it is at least four and sometimes twelve weeks before normal sweating is restored and the patient can undertake exertion without discomfort. In some instances the disease progresses and the subject is exhausted by the slightest effort. One attack does not confer immunity.

The pathogenesis of the goose-flesh-like rash has been described independently by Sulzberger and others<sup>12</sup> and by O'Brien.<sup>7</sup> Here it need only be pointed out that each vesicle is caused by the localized escape of sweat into the dermis from a blocked, ruptured sweat duct. The

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14. Clinically the lesions simulate papules. Histologically<sup>7</sup> they are vesicles and are due to localized extravasations of sweat into the dermis.

clinical and histologic evidence has shown conclusively that the rash and the associated anhidrosis are the end results of previous miliaria. Indeed, the rash represents the chronic phase of occlusion of the sweat glands, the acute phase being miliaria rubra itself. New descriptive terms seem to be required for the lesions other than the well known vesicles and papules of miliaria. Henceforth the lesions which resemble goose flesh are called anhidrotic vesicles. The rash is called the anhidrotic rash,<sup>15</sup> whereas the associated anhidrosis is called tropical anhidrosis. The term anhidrotic asthenia is used only when the tropical anhidrosis is severe enough to cause general symptoms.

A detailed analysis of the symptoms and signs noted in the present series of cases is given in panel D of table 1. The subjects had been in the tropics for an average of six and a half months before they commenced to suffer from miliaria. The average interval between the commencement of miliaria and the first general symptom of anhidrotic asthenia (usually exhaustion) was eight weeks. In some cases there was no interval, that is, according to the patient both the miliaria and the general symptoms commenced together, and in others it ranged up to twenty-four weeks. This large range of variation is probably caused by a number of factors which may themselves vary and which include the current weather and the activity and the psychologic nature of the subject. However, the most important factor would appear to be the number of sweat glands implicated by the antecedent attack of miliaria. In regard to this point, most persons suffer from miliaria in only a moderately severe form, and it occurs in progressive or recurring waves which chronically obstruct groups of sweat glands in turn. When this is the case, the latent period between the onset of miliaria and the general symptoms tends to be long and indefinite. In a smaller number of cases a single attack of miliaria involves most of the sweat glands; in such instances, the latent interval is short. The interval which usually elapses between the cessation or improvement of the miliaria and the onset of the general symptoms of anhidrotic asthenia is not recorded as it varied much and was often difficult to assess from the patients' impressions. The same applies to the patients' statements on the duration of the

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15. Histologically, the vesicles and rash are perhaps more correctly described as dyshidrotic and not anhidrotic in nature. However, the word "dyshidrosis" has been used in the past for other conditions and is therefore best avoided. Moreover, the anhidrosis associated with the rash is its most significant feature, and it therefore seems necessary to suggest this relationship. A term "miliaria alba" is sometimes found in the literature (Sutton, R. L., and Sutton, R. L., Jr.: *Diseases of the Skin*, ed. 9, St. Louis, C. V. Mosby Company, 1935, p. 1185) but seems to have largely passed out of use. As no complete description is available, its affinity to the anhidrotic rash is doubtful. Nevertheless, miliaria alba and the anhidrotic rash are probably identical. Because it lacks functional significance, reintroduction of the obsolete "miliaria alba" is not recommended.



TABLE 1.—Symptoms and Signs on Exposure to Heat and Exertion (Comparative Data from All Authors)

Author and Place	No. of Cases	Exhaustion	Sensation of Excessive Heat	Headache	Vertigo	Dyspnea	Palpitation	Dimness of Vision ("Blackout") and Syncope	Gastrointestinal Symptoms
A. Wolkstein and others "Thermogenic Anhidrosis" (North American Desert)	8	+	+	+	+	Not mentioned	No mention	Two had short attacks of syncope	Nausea in a doubtful case (case 6)
B. Laddell and others "Heat exhaustion, Type 11." (Desert of Southern Iraq)	55	+	Not mentioned (can be presumed to have been present—skin hot clinically)	No mention	+	Present in 23 of 55 cases	Palpitation and precordial pain in 2 cases	Dimness of vision not mentioned; apparently no syncope	Vomiting and cramps in 4% anorexia
C. Sulzberger and others (Guam)	1	+	+	+	+	+	No mention	+	No mention
D. Present Series* (South West Pacific)	38							Dimness of vision on exertion present in about 50% of patients, usually shortly before they reported ill; occasionally complete syncope	In some cases anorexia or nausea; epigastric discomfort present in 2 cases; no vomiting or cramps
1. Average duration of symptoms before reporting ill (days)	19			21	20	14	19		
2. Range of variation (days)	2-90		Duration not recorded	1 to 90	2 to 90	1 to 30	2 to 90		
3. Percentage of cases affected	100		100	80	80	70	70		

\*The data here are calculated only from those cases in which the presence or absence of the symptom was recorded in the notes.

Anhidrosis on Clothed Areas	Anhidrotic Rash (Goose-Flesh-Like Rash)	Profuse Sweating on Forehead and Face	Frequency and Polyuria	Miliaria	Desquamation	Pilocarpine Test	Enlarged Lymph Glands	Miscellaneous
A. +	+	+	No mention	Definite history in 1 case; no note in remainder	In long-standing cases	No response on dry areas	No mention	Onset of disease seemed sudden; condition improved as rash disappeared
B. History of "defective sweating" in 87%; "dry skin" on examination in 40%	No specific mention; "lichenification"; prickly heat in "healing or desquamating" stage	+	Definite and extremely common	80% had rash on admission to the hospital; moderately severe or severe	Severe	Apparently not used	No mention	Tachycardia; insomnia; duration in hospital, 10 to 20 days
C. +	+	+	Indefinite	Extremely severe	Not mentioned	Not mentioned	Tender; enlarged?	
D. Partial or complete in 100% of cases	Present in 100% of cases on dry parts	All cases	Present but not conspicuous	History in all except 2 cases, in which the patients denied having had rash of miliaria; approximately 25% still had symptoms or signs of miliaria on admission	Present but not severe	No response on anhidrotic areas	Axillary and inguinal in 60%; axillary or inguinal in 7%	Duration of illness: some weeks; insomnia uncommon and due only to itch

anhidrosis.<sup>16</sup> General symptoms were present for an average of two to three weeks before the patients reported ill. It is of interest that anhidrotic asthenia developed in 1 subject within two months of his arrival in the tropics; the mean period was eight and a half months.

Apart from the main symptoms given in table 1, certain less common symptoms may have physiologic relevance. In 4 cases there were swelling and subjective tightness in the hands, particularly in the fingers (intracutaneous edema?).<sup>17</sup> Nosebleed was noticed in 1 case and in another some tenderness of the inguinal lymph glands after exercise. Paresthesias of the extremities were rarely present and never severe. Signs of congestive heart failure were not seen. In no instance was there any evidence of dehydration or of abnormal thirst. As contrasted with those with the congenital disease, few subjects learned to moisten their clothes to obtain a degree of relief.

Observations on the blood pressure before, during and after exercise were not sufficiently detailed to warrant the statement that it is significantly altered as compared with that in normal controls. Clearly, many observations would be required for the compilation of reliable figures. In a few experiments I found that the blood pressure immediately after exercise showed no gross alteration when compared with the same subject's resting level. It is possible that this finding is an abnormality in itself, as a rise in company with exercise is expected. On the other hand, Sulzberger and others<sup>12</sup> noted a substantial rise in the systolic blood pressure immediately after exertion. Although no figures are available, it is presumed that the blood pressure falls dramatically in the rare instances of fainting. The findings of Ladell and others in relation to blood pressure will be given later when their work is discussed.

Many subjects had an eosinophilic leukocytosis in the apparent absence of an accepted cause. However, in a few no eosinophilia was present, and as the observations were not sufficiently extended no conclusions can be drawn. Nevertheless, it is worth recording that eosinophils are frequently found in good numbers in sections of skin affected by tropical anhidrosis. It would be of much interest if the various sequelae of miliaria could be proved to be causes of eosinophilia in the tropics.

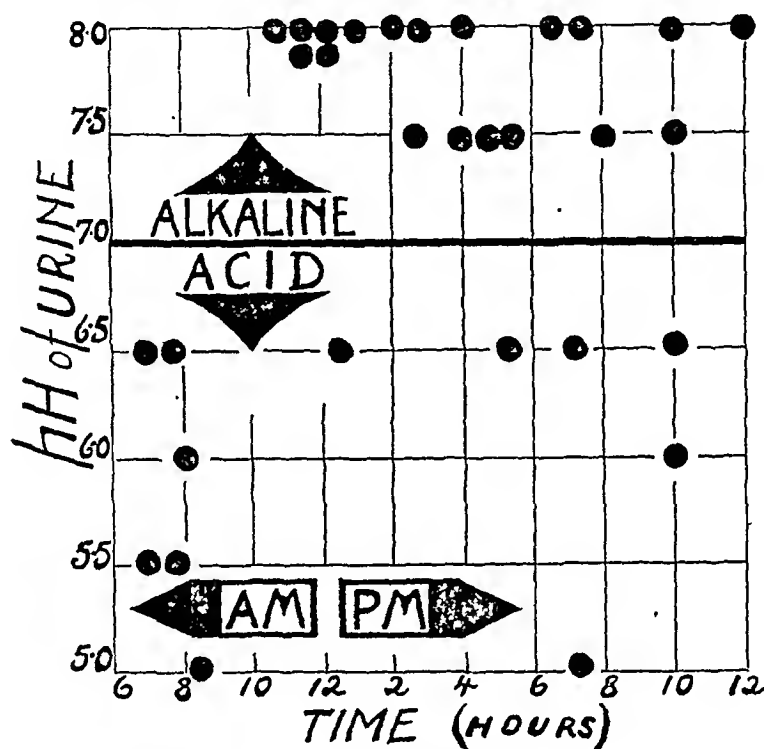
As regards the physiologic disturbance in anhidrotic asthenia, it can be presumed that the anhidrosis leads to a diminution in the fluid loss from the skin and to an associated change in fluid balance. Although no

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16. The duration of the preceding anhidrosis was noted by Ladell and others<sup>5</sup> to vary in the desert from "many days" to three weeks.

17. It is of interest that L. W. Eichna, W. B. Bean, W. F. Ashe and N. Nelson, (Performance in Relation to Environmental Temperature: Reactions of Normal Young Men to Hot, Humid [Simulated Jungle] Environment, *Bull. Johns Hopkins Hosp.* 76:25 [Jan.] 1945) record swelling of the hands in normal subjects under heat stress.

precise work was possible under service conditions, it is thought that most of the fluid adjustments take place in the early stages of the disease before advice is sought. However, some polyuria may continue after the patients report ill. Allen<sup>18</sup> found that the average daily fluid intake (exclusive of that in solid food) in 2 cases observed over six days was 1,800 cc. The corresponding urinary output was 1,680 cc. In 1 of these cases the average specific gravity of single specimens collected over the same six days was only 1.009. The relatively large volume and low



Tropical anhidrotic asthenia. The diurnal variation in the reaction of urine passed, over a period of six days, by a resting hospital patient. The large number of  $p_H$  readings at or above 7.5 during the heat of the day is noteworthy. (The  $p_H$  is estimated by a range of indicators.)

specific gravity of the urine<sup>19</sup> indicate that more fluid than normal was lost by way of the kidneys. Further, the small difference between the fluid intake and the urinary output confirms the curtailment of fluid losses through the skin.

In Ladell, Waterlow and Hudson's<sup>5</sup> cases more obvious polyuria and frequency occurred. They found an average daily urinary output of 2,724 cc.; 2 patients excreted 8,000 cc. per day. When these figures are compared with Allen's, it should be remembered that the degree of polyuria depends not only on the diminution of one avenue of water excretion by the anhidrosis but also on the individual patient's fluid

18. Allen, S. D.: Personal communication to the author.

19. The average normal daily volume of the urine in the humid tropics is 500 to 1,000 cc., figures toward the lower range being more common. Figures for specific gravity below 1.015 are not expected.

intake. According to the intake figures given by Ladell and his colleagues (an average of 7,000 cc. per day), it would seem that their patients maintained a considerably higher intake than is common in the humid zones. I doubt whether many soldiers in the South West Pacific voluntarily maintained an intake of anything like 7,000 cc. per day. This agrees with the usual belief that fluid losses and thus fluid requirements are greater in an equivalent dry climate.<sup>20</sup> It would therefore seem that this apparent difference in polyuria is largely, if not wholly, explicable on the basis of different levels of fluid intake.<sup>21</sup>

Sulzberger and his colleagues<sup>12</sup> give a chart on the fluid, salt and nitrogen balance in their case. Their figures, when compared with those found for normal controls, lead them to suggest that their patient lost as much sweat from his hyperhidrotic areas as the controls lost from their whole bodies. However, as their figures for fluid balance differ from those of other observers, this suggestion should not be accepted as applying generally.

Allen<sup>18</sup> has made some interesting observations on the reaction of the urine; his readings for one typical case are given in figure 1. The patient was at almost complete rest. It will be seen that under such conditions there is evidence of alkalosis during the heat of the day.

The mode of the production of the symptoms and signs of the disease is a subject for speculation. That the anhidrosis is basically responsible can hardly be denied; the means by which it leads to pathologic changes, such as the extreme dyspnea and tachycardia on exertion, is another matter. Various factors probably play a part, and it is thought that the explanation is complex. It can perhaps be presumed that the diminished secretion of sweat onto the cutaneous surface as a whole leads to diminished heat loss and consequent heat retention. But the resulting pyrexia is surprisingly slight and hardly enough to cause much distress on its own account. Further, when the clothes are damped with water to substitute for the absent sweat, the syndrome is still evoked by exercise, though in my opinion it is thereby delayed in its onset and is less severe.

The dyspnea and tachycardia lead one to believe that the circulation of the blood is disturbed. In the absence of any evidence that the heart itself is abnormal, emphasis is naturally placed on an abnormality of distribution of the blood. It seems more than likely that the effective

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20. Lee, D. H. K.: *A Basis for the Study of Man's Reaction to Tropical Climates*, University of Queensland Papers, Department of Physiology, 1940, vol. 1, no. 5, p. 15.

21. Alkalosis can cause diuresis (Bazett, H. C.: *Studies on the Effects of Baths on Man: Relationship Between the Effects Produced and the Temperature of the Bath*, *Am. J. Physiol.* 70:412 [Oct.] 1924). However, such an effect is probably not significant in the disease under discussion.

blood volume is diminished by excessive dilatation of the peripheral vessels to such an extent that the circulation cannot meet the needs of both muscles and skin during exercise. In conformity with this view is the general congestion seen in tissue sections. Clinically, however, there is little or no erythema, the congestion being obscured by the whitish anhidrotic vesicles and the generalized edema of the skin. If severe miliaria is still present, the skin is obviously red.

As concerns the presumed peripheral circulatory failure, it is significant that Dill<sup>22</sup> postulated the same concept in regard to the fatigue responses of subjects working in impervious clothing, conditions which are tantamount to those of intrinsic anhidrosis.

In previous papers (Allen and O'Brien,<sup>6</sup> O'Brien<sup>7</sup>) it has been suggested that sweat is reabsorbed into the blood from the anhidrotic vesicles in amounts which are probably considerable and that this resorption may in some way contribute to the production of the abnormal effect of exercise. Sulzberger and others<sup>12</sup> have rightly criticized this suggestion in so far as exercise produces a similar clinical picture in those suffering from a congenital absence of the sweat glands. Nevertheless, the "internal circulation of sweat" is an interesting phenomenon and should not be forgotten in any discussion of the abnormal physiology. Experiments designed to evaluate the possible toxicity of sweat would be of interest in this connection.

It was at one time thought that the hyperpnea might represent a true panting response, a compensatory device enabling a greater loss of water, and thereby heat, via the respiratory system. This suggestion that a change to the canine method of losing heat occurs is intriguing and has been postulated before in explanation of the tachypnea in extreme experimental overheating.<sup>23</sup> In less severe conditions the response is not elicited.<sup>24</sup> Certainly no direct evidence in its favor has been forthcoming in this particular disease. If the hyperpnea were a panting effect some clinical alkalosis might be expected, but in the present cases no evidence of tetany, overt or latent, no definite paresthesias, no carpopedal spasms and no positive Trousseau or Chvostek sign has been demonstrated.

Ladell's<sup>5</sup> Iraq cases afford the most suggestive indication of possible latent tetany; 8 of 55 patients complained of numbness and tingling in the limbs. But such evidence on its own is hardly convincing, especially as tetany due to hyperventilation is possible, as an incidental phenomenon, under any conditions of stress. For instance, frank tetany can

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22. Dill, D. B.: The Economy of Muscular Exercise, *Physiol. Rev.* **16**:263 (April) 1936.

23. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 954.

24. Lee,<sup>20</sup> p. 29.

occur in classic heat exhaustion.<sup>25</sup> Unfortunately the conditions under which the present work was carried out did not allow any chemical examinations to be made. Ladell and others in their studies of anhidrotic asthenia found no definite changes in the blood acid-base equilibrium, but they themselves stated that their observations were not sufficiently exhaustive to justify a final decision on this point.

Sulzberger and his co-workers<sup>12</sup> have recently responsored the idea that an alkalosis due to panting is the direct cause of some of the symptoms and signs, and they specifically cited the dizziness and fainting. They offered support in the demonstration of a fall in the serum content of combined carbon dioxide during static exposure to heat. However, they failed to find an associated change in the blood  $p_H$ , though their figures for  $p_H$  were persistently at the top of the normal range (7.50). Moreover, they, like other workers, failed to find any clinical sign of even latent tetany. It is perhaps reasonable to expect a fall in the combined carbon dioxide content of the blood in association with the abnormal hyperpnea. However, there is as yet no adequate reason to suppose that any secondary acid-base changes in the blood are habitually uncompensated to a significant degree. Indeed, a further point to be considered in particular relation to exercise is that the acid metabolites produced during muscular activity must tend to counteract any incipient alkalosis due to heat. If, as is thought, a relative deficiency of circulation occurs during exercise, a simultaneous excessive acidosis due to anoxemia is theoretically possible. Clearly there is much scope for inquiry into the acid-base balance of these subjects during both work and rest in heat.

Even if frank tetany regularly occurred during exercise, there still remains the more fundamental doubt that the hyperpnea is a true panting response. Although convenient, such a concept surely exaggerates the sequence of events into a semiphysiologic "mechanism" whose supposed function is to make up for the failure of the skin by an increase in the respiratory heat loss. To give the hyperpnea such a high and complex status seems presumptuous at this stage, particularly when a circulatory disturbance could be a simpler and more direct cause. Moreover, it should not be forgotten that the breathing is not of the shallow panting type. In any case, the suggestion by Sulzberger and his colleagues that an efficacious method of respiratory heat loss exists is contradicted by their own figures for water balance, which indicate, rather unexpectedly, that little or no extra water (and therefore heat) is lost from the respiratory system in tropical anhidrotic asthenia.<sup>26</sup>

25. MacLean, K. S.: Observations on Sunstroke and Heat Exhaustion in the Tropics, *J. Roy. Nav. M. Serv.* 29:31 (Jan.) 1943.

26. As a matter of interest, F. W. Sunderman (Persons Lacking Sweat Glands: Hereditary Ectodermal Dysplasia of Anhidrotic Type, *Arch. Int. Med.* 67:846 [April] 1941) obtained similar results when studying water balance in the congenital type of the disease.

To conclude this discussion on the proposed role of alkalosis in anhidrotic asthenia, some work of Rice and Steinhaus<sup>27</sup> may be interesting if not fully applicable. In the knowledge that the dog differs from normal man in being prone, when overheated by strenuous work, to an alkalosis from panting, they showed that if the dog is exercised by swimming in water which is sufficiently cool to prevent overheating true panting no longer occurs. What is significant is that the dog's acid-base balance then comes to resemble closely that of man in that acidotic tendencies predominate. The converse possibility therefore suggests itself, i.e., does man, when rendered anhidrotic like the dog, come to share that animal's normal panting and alkalotic reactions? In the formulation of an answer, it is worth recalling that whereas tetany is prone to develop in normal man during overbreathing not once has it been seen as a complication of anhidrotic asthenia.

Ladell and others do not discuss the question of alkalosis, and it is likely that they too thought it unimportant. They simply propose that the respiratory distress of anhidrotic asthenia is due to the stimulating effect of a raised blood temperature on the respiratory center. Even this suggestion is not entirely acceptable in so far as no such gross distress is produced by exercise in otherwise normal subjects whose temperatures are raised to the same degree by some form of toxemia. This is not to deny that pyrexia stimulates the respiratory center; what has to be explained is the severe dyspnea which these anhidrotic patients experience on moderate exertion. The demonstration by Bazett and Haldane<sup>28</sup> and by Landis, Long, Dunn, Jackson and Meyer<sup>29</sup> that the respiratory minute volume during hot bath experiments depends not only on the height of the body temperature but also on the rate of its increase may help to explain the discrepancy. During activity, the temperature of anhidrotic subjects can climb by as much as 2 degrees F. (1.1 degrees C.) within a few minutes.

Relevant to the pyrexia of anhidrotic asthenia is the debatable question of the "normal" upper limit of body temperature in the tropics. In this regard the study of Renbourn and Bonsall<sup>30</sup> on residents of Northern India is of interest, for figures on the order of 101 F. (38.3 C.)

27. Rice, H. A., and Steinhaus, A. H.: Studies in the Physiology of Exercise: V. Acid-Base Changes in the Serum of Exercised Dogs, *Am. J. Physiol.* **96**:529 (March) 1931.

28. Bazett, H. C., and Haldane, J. B. S.: Some Effects of Hot Baths on Man, *J. Physiol.* **55**:iv (March) 1921.

29. Landis, E. M.; Long, W. L.; Dunn, J. W.; Jackson, C. L., and Meyer, V.: Studies on the Effects of Baths on Man: III. Effects of Hot Baths on Respiration, Blood and Urine, *Am. J. Physiol.* **76**:35 (March) 1926.

30. Renbourn, E. T., and Bonsall, F. F.: Observations on Normal Body Temperatures in North India, *Brit. M. J.* **1**:909 (June 15) 1946.



for the rectal temperature were often recorded. Likewise, wharf laborers in the tropics can show similar grades of pyrexia (Breinl).<sup>31</sup> However, it must be conceded that the heating effect of miliaria of varying degrees of severity was either not specifically or not completely taken into account in these two studies. Nevertheless, even in laboratory experiments in which the presence of miliaria can be excluded normal acclimatized subjects commonly show temperatures on the order of 101 F. after exercise tests. In fact, Eichna, Ashe, Bean and Shelley<sup>32</sup> inferred that 101 F. should be regarded as the normal upper limit of physiologic response to work in heat. It would thus seem that in anhidrotic asthenia exhaustion ensues during work before the temperature climbs to a striking level and that therefore the pyrexia per se does little to explain the symptomatology.

#### LITERATURE ON ANHIDROSIS IN RELATION TO HEAT DISORDERS

There exist many accounts of subjects with a congenital absence of the sweat glands, their disease usually being called hereditary ectodermal dysplasia of anhidrotic type. The symptoms and signs which these persons show when exposed to heat are similar to those of the acquired disease described in this paper. For instance, Thannhauser's<sup>33</sup> patient suffered from exhaustion, palpitation, dyspnea and tremor. Sunderman's<sup>34</sup> 3 patients complained of headache and "fever" and showed hyperpnea, tachycardia and diuresis when exposed to high temperatures. It is interesting that the highest oral temperature which Sunderman recorded was only 102 F. (38.9 C.), a temperature comparable with that found in cases of anhidrotic asthenia. However, Hiebert and Garland<sup>35</sup> found that the temperature of the skin was abnormally high; in a child patient it was as high as that found in a normal child with an internal temperature of 104.5 F. (40.3 C.).

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31. Breinl, A.: An Inquiry into the Effect of High Wet Bulb Temperatures upon the Pulse Rate, Rectal Temperature, Skin-Shirt Temperature and Blood Pressure of Wharf Labourers in North Queensland, *M. J. Australia* 1:303 (April 16) 1921.

32. Eichna, L. W.; Ashe, W. F.; Bean, W. B., and Shelley, W. B.: The Upper Limits of Environmental Heat and Humidity Tolerated by Acclimatized Men Working in Hot Environments, *J. Indust. Hyg. & Toxicol.* 27:59 (March) 1945.

33. Thannhauser, S. J.: Hereditary Ectodermal Dysplasia of the "Anhidrotic Type," with Symptoms of Adrenal Medulla Insufficiency and with Abnormalities of Bones of Skull, *J.A.M.A.* 106:908 (March 14) 1936.

34. Sunderman, F. W.: Persons Lacking Sweat Glands: Hereditary Ectodermal Dysplasia of Anhidrotic Type, *Arch. Int. Med.* 67:846 (April) 1941.

35. Hiebert, J. M., and Garland, J.: Hereditary Ectodermal Dysplasia of Anhidrotic Type, *New England J. Med.* 210:84 (April) 1934.

In other accounts, for instance in MacQuaide's,<sup>36</sup> there is mention of fainting on exposure to the sun. These subjects habitually avoid exposure or work in the heat, and they typically wet their clothes or bathe frequently in order to ameliorate their symptoms in hot weather. One such patient of de Silva's<sup>37</sup> bathed more than twenty times a day.

The skin in these cases of congenital disease is not only dry but also thin, glossy, pliable, somewhat wrinkled and transparent. From the descriptions, it is apparent that neither a miliarial nor an anhidrotic rash is present; this observation tallies with the complete absence of eccrine sweat glands and their ducts in tissue sections. Microscopically, the sebaceous glands and hairs may also be absent.

There is an account by Fog<sup>38</sup> of a young Dane in whom a diffuse anhidrosis developed after paratyphoid. The symptoms were inability to work in the sun associated with a feeling of excessive heat, dull pain in the precordium, palpitation, dyspnea, polyuria and, unlike most typical cases of anhidrotic asthenia, painful paresthesias of the limbs and face. The skin was "dry and scaly." There is no note of preceding or concurrent miliaria. Fog believed that the anhidrosis originated in the central nervous system, but a reading of his paper suggests that despite the long history (six years till the time of examination) the disease was caused by a peripheral obstruction of the sweat glands analogous to that in tropical anhidrotic asthenia.

Fog studied his case fully, and his observations seem pertinent to the tropical disease. When the patient was placed in a hot chamber, a condition thought to be circulatory insufficiency developed. Rales appeared in the lungs, a feature which no other author has noted. More typical of tropical anhidrotic asthenia is that the clothed subject showed a pulse rate of 185 beats and a respiratory rate of 55 excursions a minute while he was undergoing an ergometer experiment of only mild severity under moderate atmospheric conditions. However, in spite of extreme subjective distress, his temperature rose only 0.1 degree C. (0.2 degree F.). Also possibly significant in relation to tropical anhidrotic asthenia is the observation that at about the time the symptoms and signs began the blood pressure fell, despite the continuance of the exertion, to approximately the preexercise level. The subject could work much more efficiently provided he wore scanty clothing and the surrounding air was kept moving by a fan. Fog concluded that the

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36. MacQuaide, D. H. G.: Congenital Absence of Sweat Glands, *Lancet* 2:531 (Oct. 21) 1944.

37. de Silva, P. C. C.: Hereditary Ectodermal Dysplasia of Anhydrotic Type, *Quart. J. Med.* 8:97 (April) 1939.

38. Fog, M.: General Acquired Anhidrosis: Report of a Case and Investigations of the Heat Regulation and Circulation, *J.A.M.A.* 107:2040 (Dec. 19) 1936.

heart was not responsible for the circulatory upset, and he placed stress on a peripheral dilatation of the vessels, a general conclusion which, as has been noted, seems to apply to tropical anhidrotic asthenia.

Engelhardt and Melvin<sup>39</sup> described a rather similar instance involving an American white woman aged 49 who had had anhidrosis with lowered heat tolerance for sixteen years. The only preceding disease was typhoid in her youth. At the time of examination she had a red papular rash on the legs which, although not fully described, may have been of a miliarial nature. The photomicrograph of a skin section is not easy to interpret, but it seems to suggest the presence of a keratin plug similar to those described in cases of tropical anhidrosis and anhidrotic asthenia.<sup>7</sup>

In the two accounts just cited there is no indication whether the anhidrosis was confined to the covered parts, as in tropical anhidrotic asthenia, or whether anhidrotic rashes were present. However, a letter by Blank<sup>40</sup> in response to the paper of Wolkin and others<sup>4</sup> implies that genuine tropical anhidrotic asthenia has been observed at times among civilians in the United States of America.

As contrasted with these few accounts of the acquired disease in the subtropical zones, reports are much more definite in their incrimination of anhidrosis as a common and notable cause of failure of heat adaptation in the tropics. However, until the recent war no clear account of anhidrotic asthenia as distinct from the other heat disorders appeared to exist. Except as an acute symptom in cases of actual heat hyperpyrexia, the role of anhidrosis is mentioned rather obliquely or in passing. The association of failure of adaptation with the anhidrosis produced by miliaria is certainly not stressed in any account that I can find. The most suggestive prewar paper is that of Hamilton, Basu and van Haeften<sup>41</sup> who found that of 20 subjects suffering from the effects of heat in Allahabad, 6 had anhidrosis of considerable duration associated with subacute general symptoms such as headache and giddiness. The most significant statement about these 6 patients is that their skins were dry and "sandy" to the touch. Although it is not much to base an opinion on, this "sandy" texture of the skin could easily have been an anhidrotic rash. The authors stated that the 6 patients were always on the verge of heat hyperpyrexia. More will be said about this last comment and of heat hyperpyrexia later.

39. Engelhardt, H. T., and Melvin, J. P.: General Acquired Anhidrosis, *Am. J. M. Sc.* **210**:323 (Sept.) 1945.

40. Blank, H.: Anhidrosis Following Exposure to Extreme Heat, *J.A.M.A.* **124**:1152 (April 15) 1944.

41. Hamilton, C. S. P.; Basu, D. N., and van Haeften, J.: Review of Cases of "Effects of Heat" (Heat Stroke, Anidrosis and Heat Exhaustion) Occurring During the Hot Weather of 1929 at Allahabad, *J. Roy. Army M. Corps* **55**:120 (Aug.) 1930.

The findings of all observers in the recent war are summarized in table 1.<sup>42</sup> The likeness of the conditions described is so great that there appears sufficient evidence to conclude that all are one and the same. At all events, it is justified to assume this as a basis for future work. The points of mutual agreement are so numerous and obvious that only the significant differences call for critical discussion. As a measure of convenience, the name anhidrotic asthenia will be used henceforth to describe the disease as observed by all writers. Later on the merits of the various proposed names will be analyzed.

Wolkin and others<sup>4</sup> gave a description of 8 soldiers who became affected in the American desert area. This team is the only one to stress the existence of a period of generalized hyperhidrosis (excessive sweating) prior to the onset of the cessation of sweating. It is probably unwise to accept this conclusion without reserve. In the first place it is always hard to decide, even on close examination, when free sweating becomes excessive enough to justify the term "hyperhidrosis." There is a normal wide range of secretory power among persons subjected to the same conditions, and some healthy persons sweat extremely freely. Moreover, I have found that patients' statements on their sweat function are untrustworthy and that even intelligent people tend to pay little attention to this aspect of health. Furthermore, the profuse head sweating which develops in anhidrotic asthenia simultaneously as the rest of the body becomes dry often deludes the patients into believing that the whole body sweats intensely. All observers agree that excessive sweating does in fact occur from the face and forehead during the course of the disease, but I have not observed to my satisfaction an unequivocal, general hyperhidrosis preceding the anhidrotic phase, and, as suggested, there is doubt as to the criteria which enable such a hyperhidrosis to be either defined or assessed.

This question of a preceding general hyperhidrosis is not academic, as Wolkin and others go on to argue that the excessive function involved may be thought of as overtaxing the sweat mechanism to the extent of producing a "temporary functional paralysis." Indeed, this is their opinion as to the origin of the anhidrosis. Apart from the doubt that a general preliminary hyperhidrosis does occur and that it can exhaust the sweat function, no direct evidence is available that the sweat mechanism is actually paralyzed in anhidrotic asthenia. Such evidence as is available<sup>7</sup> is in favor of an entirely different concept, namely, that the glands, despite some dilatation, are active and that the sweat produced is unable to reach the cutaneous surface simply because of organic obstructions (keratin plugs) at the sweat pores on the covered parts of

42. Whereas R. G. Park (*Disorders Due to Heat*, New Zealand M. J. 44:128 [June] 1945) fully recognizes the general importance of anhidrosis in the tropics, he does not define the entity under discussion.

the skin. It is of course possible, and this is not the point under dispute, that sweating may play a role in causing the fundamental preceding blockage of the pores, that is, the primary histologic lesion of the antecedent miliaria.<sup>7</sup>

In all Wolkin's cases the condition seemed to begin comparatively suddenly, the whole disease coming on over only a few days. Even if this observation is correct and needs no modification from the knowledge that, until the subject works, the disease can be latent, the speed of onset of symptoms is not regarded as a point of fundamental distinction; the malady is essentially the same whether the pores close concurrently or progressively. In all the 8 cases reported by Wolkin and others the disease was severe; indeed, it was apparently by means of its severity that the disease was readily segregated from other heat disorders. If these writers had found and studied cases of less severity, and they inferred that some probably occurred within their available clinical material, they would perhaps agree that in many instances the disease tends to be subacute in its onset, the subject hardly knowing when he first becomes ill. It is, of course, possible that the disease may actually begin more suddenly in the desert than in the humid climate. This is a point which is difficult to elucidate, but I believe that if there is such a true difference it is bound up with a corresponding more fundamental difference in the nature of miliaria in the two climates. In this regard, Wolkin and his co-workers did not observe the etiologic role of miliaria; they noted without comment a history of miliaria some ten days before in their case 5. Yet, credit must go to them for emphasizing the importance of the anhidrotic skin. All their subjects almost certainly had the anhidrotic rash which is now known to be conclusive evidence of antecedent miliaria.<sup>7</sup> In a description of the rash, they mentioned its most striking feature, i.e., its superficial similarity to goose flesh. However, they do not comment on its production by heat and exertion and its disappearance on cooling. It is worth pointing out that these observers say little of local cutaneous symptoms. This corroborates the point that the distressing pruritus of miliaria has nearly always passed away by the time general symptoms arise. An alternative explanation is that the authors may have felt that the presence or absence of miliaria was not worth comment. It is not certain from their account whether the specialized sweat glands of palms and soles, axillas and groin were out of action in their material.

Under the name "heat exhaustion, type II, Ladell, Waterlow and Hudson<sup>5</sup> describe fully, and to some extent in a complementary way, the syndrome as they saw it among troops in the desert of Southern Iraq. The disease, which lasted some ten to twenty days, occurred chiefly toward the end of the summer, when the worst weather was over and cases of the classic heat disorders were no longer frequent. I also

have noted a similar association with the end of the wet season in the humid zones and believe it is due to the fact that miliaria is mild or absent in the early hot weather but gradually increases in severity and incidence with the progress of the season.

In general, the disease as found in the desert by these observers was identical, except for minor variations, with that described herein. In 80 per cent of cases there was a history of moderately severe or severe miliaria a short time previously. Moreover, 87 per cent of the patients gave a history of defective sweating. On examination, the covered parts of the skin were classified as "dry" in 40 per cent of cases. This is a much lower proportion than that found in my own work (all cases), and hardly tallies with their own note of a history of defective sweating in 87 per cent. I suggest that had a starch-iodine or similar preparation been used more than 40 per cent of their patients would have been found to have a significantly large proportion of sweat pores blocked. It should be realized that one difficulty in assessing the presence of an incomplete anhidrosis of the covered parts is that any remaining unaffected sweat glands secrete vigorously and thereby mask the presence of even numerous blocked glands. Therefore, in cases with incomplete dryness one should either perform a starch-iodine or similar test or, as has been suggested,<sup>7</sup> simply estimate the density of the various pore lesions on the skin as a whole after exercise; every anhidrotic vesicle, miliarial vesicle and papule indicates a corresponding obstructed sweat gland.

Ladell and others do not record seeing the anhidrotic rash. Indeed, in a more recent note Waterlow<sup>43</sup> stated that it was definitely not present. As much importance is attached to the changes in the skin for diagnostic and other reasons, this lack of correlation deserves comment. It is noteworthy that Wolkin and others describe the presence of the rash in their cases, which like Ladell, Waterlow and Hudson's, occurred in a dry climate. The latter seem to have given a partial description of such changes when they mentioned the presence of miliaria in the "chronic, healing, desquamating" stage, with "lichenification." In the humid zone this is precisely the stage of miliaria which is associated with the production of the anhidrotic rash on exertion. I feel that this lack of agreement between Ladell's team and other writers resides more in terms than in reality and that the former actually saw the anhidrotic rash but preferred to call it "healing prickly heat." However, it must be conceded that this disagreement may possibly be explicable on other bases. Perhaps Ladell and his colleagues did not exercise their subjects sufficiently before they observed their skins. Perhaps they saw the rash but ignored it because of its similarity to the commonplace goose flesh. Again, general symptoms may ensue in the desert when the miliaria is in a more

<sup>43</sup> Waterlow, J., in Allen, S. D., and O'Brien, J. P.: Tropical Anidrotic Asthenia: A Preliminary Report, *Bull. War Med.* 5:486 (April) 1945.

acute stage, in which case it is proposed that these authors would have seen the development of the anhidrotic rash if they had watched their subjects for a longer period during the skin-healing phase.

That an earlier onset of general symptoms, relative to the stage of the cutaneous lesions, may be the true explanation of the disparity is supported by Ladell's note that 80 per cent of his patients had a still recognizable miliaria. In my experience in the humid zones, and incidentally in Wolkin's in the desert, the cutaneous rash had progressed so fully to the anhidrotic stage that its miliarial origin was by no means obvious and had to be proved by the detailed clinical and histologic work reported elsewhere.<sup>7</sup> There is the final possibility that desert miliaria follows a different course or is a significantly different disease from the variety in the humid areas. I have no experience of the former, so that I cannot base an opinion on direct observation. However, it does seem that such an assumption would, in the present state of our knowledge, complicate matters still further. An examination of published reports does not indicate that a useful purpose would be served at this stage by maintaining that two different diseases masquerade under the name "miliaria rubra." It would appear from the literature that miliaria leads to anhidrosis in the desert just as certainly and in the same way as it does in the humid zones. This is surely the main issue beside which all others fade into insignificance. Slight differences in miliaria as it occurs in the two climates may be admitted; for instance, according to Ladell's account, postmiliarial desquamation is relatively more obvious in the desert zones.

The highest rectal temperature found by Ladell and others was 100.9 F. (38.3 C.), a figure which is consistent with all those already cited. The skin temperatures were relatively high, as was suspected in the earliest observations;<sup>8</sup> for instance, the dry skin of a patient registered a temperature of 100 F. (37.8 C.), while under the same conditions the sweating skin of a control (who incidentally had a mild local miliaria) gave a reading of 95.1 F. (35.1 C.). In hot chamber experiments the rectum-skin temperature gradient was decreased as compared with that in controls. The elevated temperature of the skin can be presumed to be mainly due to a lack of cooling in the absence of effective sweating.

Some observations were carried out by Ladell and others on the blood pressure though not on any changes produced by exercise. The average systolic blood pressure of recumbent patients was 20 mm. higher than that in normal controls, and the pulse pressure was raised. The diastolic pressure varied greatly, being persistently low (40 to 50 mm.) only in some cases. Capillary pulsation was frequently seen (it has not been remarked on in the humid zones). The capillary pulsation

and the increased pulse pressure are consistent with a greatly increased blood flow to the skin. The increased systolic blood pressure, which was apparently more constant than a diminished diastolic pressure, is likely to be due to increased force of ventricular contraction.

There is mutual agreement between all observers that dehydration does not occur in tropical anhidrotic asthenia, and in my view there is little or no evidence of a true deficiency of sodium chloride. In crude testing of the urine, sodium chloride was consistently present in Allen's<sup>18</sup> cases. Ladell and others found that although the chloride concentration in the urine was reduced (presumably due to the diuresis), the total daily chloride excretion averaged 3.47 Gm. (as sodium chloride). Added salt given to a test group was not retained and was excreted at once in the urine, this observation supporting the absence of a true deficit of sodium chloride. The routine chloride intake of these patients was not definitely noted but was apparently in excess of 20 Gm. per day.<sup>44</sup> In groups of fit men on an intake of the same amount the urinary chloride output varied between 3 and 6 Gm. depending on the weather. The Iraq team also found that the extra salt given to half of their patients did not increase the rate of gain in weight over that in control cases.

Ladell and his co-workers produced some evidence in favor of a reduction of the chloride level in the blood, particularly in the plasma. On the other hand, Sulzberger and others<sup>12</sup> found that as the combined carbon dioxide content of the serum fell the chloride content showed a slight and perhaps negligible rise. Clearly the blood chloride may be influenced in different ways by several factors, among which are reduction in blood bicarbonate and disordered fluid balance.<sup>45</sup>

Ladell and others emphasized that many of their patients with unclassified effects of heat had some of the symptoms of anhidrotic asthenia. Moreover, they found every gradation between the fully developed disease and mere exhaustion and weakness. Indeed, Waterlow<sup>43</sup> goes so far as to state that this disease was "by far the commonest disability produced by heat in the desert and, although not severe or dangerous, caused great loss of time and efficiency among troops." This forcible summary also expresses my experience in the humid zones, where the disease is almost commonplace if the subacute cases are taken into account. It is suggested that many of the unclassified cases of the effects of heat will be better understood if more attention is given to the state of the sweat function and, in particular, to the presence and extent of

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44. These chloride balance figures are in conformity with the high chloride concentration of such sweat as is secreted by these patients.

45. Unfortunately no evidence is available to show that an abnormally high blood volume occurs in this disease. Comparative studies of blood volume, hematocrit values and similar figures would be of interest in this regard.



miliarial and anhidrotic rashes. Classification will continue to be more difficult in areas of dry climate because the other forms of heat disease (heat stroke and classic heat exhaustion) are more prevalent and therefore cause greater confusion in such areas.

Discussing the question of etiology, the Iraq team suggested that as these anhidrotic patients secrete on their sweating areas a sweat of high chloride concentration (averaging 0.53 per cent as sodium chloride) the basis of the perverted sweat function may be "fatigue" of the sweat glands. In other words, they arrived at much the same opinion concerning the cause of the anhidrosis as did Wolkin and others. However, they also noted that in healthy controls as well as in patients with classic heat exhaustion (type I) the chloride concentration of sweat rises with the progress of the hot season. They observed that "normal" controls secrete less sweat at the end of the season than they do at the beginning. I propose, as a basis for future observation, that all these various changes in sweating owe their origin, at least partly, to the progressive blocking of sweat glands in association with miliaria, and I further propose that in all instances the changes in the chloride concentration of the sweat are due to compensatory hyperactivity of the relatively healthy unobstructed glands. For, as such glands are presumably acting to their greatest capacity, they tend to secrete a sweat which involves the least amount of osmotic work, that is, a sweat which has, like plasma, a relatively high content of chlorides.<sup>46</sup> I doubt whether the term "fatigue of the glands" is justified on the available evidence when reference is being made to these various adjustments of sweating in anhidrotic asthenia and in related obstructive states; it could equally well be argued that the chemical changes in the sweat are wholly compensatory because active secretion continues from normal glands in such instances for as long as they remain unblocked by miliaria. At all events, I have not seen in the humid zones an anhidrosis involving skin which appears otherwise normal. That is to say, anhidrosis appears to be always associated with

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46. As the sweat chloride concentration normally falls during acclimatization (Dill, D. B.; Hall, F. G., and Edwards, H. T.: Changes in the Composition of Sweat During Acclimatization to Heat, *Am. J. Physiol.* **123**:412 [Aug.] 1938), these various rises in concentration suggest, on their own face value, a process of "deacclimatization" which involves even "normal" controls. It is likely that the increased skin and rectal temperatures which accompany miliaria and its sequelae are the basic indicative factors responsible for the associated high sweat chloride concentration, for in their summary of present knowledge R. E. Johnson, G. C. Pitts and F. C. Consolazio (Factors Influencing the Chloride Concentration in Human Sweat, *Am. J. Physiol.* **141**:575 [June] 1944) have shown that in general the skin and rectal temperatures are the most potent factors controlling the sweat chloride concentration. A rise in either the skin or the rectal temperature results in a rise in the chloride concentration. It is tempting to believe that the rectal temperature, and perhaps the skin temperature, produces this effect by involving an increase in the rate of sweating from individual sweat glands.

obvious obstruction in the form of miliaria, an anhidrotic rash or ichthyosis. As a final point, when the obstruction at the pores in the last two conditions is relieved by the application of a lipid (the lipid response<sup>7</sup>), the glands discharge such a profuse, visible secretion that the idea of the existence of any form of fatigue can hardly be accepted.

Gerking and Robinson<sup>47</sup> have recently investigated this problem of possible fatigue of the sweat glands in normal "acclimatized" subjects. They found that with high rates of sweating in severe heat the sweat secretion diminished in some cases by as much as 80 per cent of the original rate in six hours even though all requirements for fluid and salt were met. These experiments are significant and certainly tend to show that the sweat glands or, more precisely, the sweat mechanism may become fatigued under extreme conditions. On the other hand, these workers did not produce a complete (local or general) anhidrosis by this method, possibly because the subjects could no longer tolerate the conditions. In similar experiments, Kuo, Takahara, Adachi and Saito<sup>48</sup> also failed to observe complete cessation of sweating. Nevertheless, the evidence for a state of relative fatigue produced by such extreme stress is fairly convincing. How else could the fall in the production of sweat be explained? It is perhaps conceivable that some of the pores could become blocked, even during the course of such short experiments; a swelling of the keratin surrounding the sweat pores might suffice. One observation by Gerking and Robinson perhaps supports the concept of activity of a local factor such as blockage of the pores, i.e., the decrease in sweating is greater under humid conditions (when the skin is bathed in sweat) than it is under dry conditions (when the skin is drier). Yet Gerking and Robinson found that moderate rates of sweating can be maintained without diminution; so it seems, on the whole, that local obstruction of the pores during short experiments, at least to a gross degree, is unlikely.

This analysis is made to demonstrate how complicated is the function of sweating. Apart from the debated question of fatigue, not only is it known that water, sodium chloride<sup>49</sup> and an intact nervous system are all required for the free formation of sweat, but the sweat glands themselves need to have completely patent pores. In fact, the sweat mechanism is probably disabled in the tropics more often by a closure of the pore

47. Gerking, S. D., and Robinson, S.: Decline in the Rates of Sweating of Men Working in Severe Heat, *Am. J. Physiol.* **147**:370 (Oct.) 1946.

48. Kuo, K. W.; Takahara, K.; Adachi, J., and Saito, K.: Sweating with Heat Stroke, *J. Orient. Med.* **22**:98 (June) 1935.

49. Taylor, H. L.; Henschel, A.; Mickelsen, O., and Keys, A.: The Effect of Sodium Chloride Intake on the Work Performance of Man During Exposure to Dry Heat and Experimental Heat Exhaustion, *Am. J. Physiol.* **140**:439 (Dec.) 1943.

than by any other means. It is therefore apparent that while short physiologic experiments in temperate climates are helpful great discretion is necessary when applying the results to the more complex conditions of long tropical residence.

To summarize, it is improbable that Gerking and Robinson's experiments on apparent fatigue shed much direct light on the obstructive type of anhidrosis. It is much more feasible that their experiments are relevant to the type of anhidrosis associated with heat stroke, for in the latter condition, soon to be discussed, the evidence is more suggestive of a true intrinsic deficiency or of failure of the sweat mechanism.

#### OBSERVATIONS ON THE DIAGNOSIS OF ANHIDROTIC ASTHENIA

As far as the humid zones are concerned, anhidrotic asthenia is readily diagnosed providing the subject is given an adequate exercise test in the heat. In the vast majority of cases the typical cutaneous lesions and the associated anhidrosis are so prominent that a confident assessment in each subject can be made. Experience of the fully developed disease facilitates estimation of the loss of adaptation caused by less general blocking of the sweat pores. Need for its differentiation from heat hyperpyrexia and from classic heat exhaustion (Ladell's type I) simply did not arise in the places in which I worked. In fact, I did not see or hear of these classic diseases affecting troops in the South West Pacific; this is not to say that cases did not occur, but at all events they must have been rare.

In the desert, where I have not worked, the problem of diagnosis is clearly more complex. Heat hyperpyrexia and classic heat exhaustion are apparently so prevalent and dramatic that they eclipse anhidrotic asthenia, although, on the evidence of Ladell and his co-workers, there is no reason to doubt that the disease does occur. Moreover, the work of these observers proves that even when other heat disorders are occurring the discrimination between them and cases of anhidrotic asthenia should be fairly readily made. However, it is subacute in its manifestations, and routine inspection of residents as they work affords the most certain method of detecting it.

Broadly speaking, three different types of heat disease, two of which are classic, and the third new, can be differentiated: (1) heat hyperpyrexia (heat stroke), (2) classic heat exhaustion (Ladell's type I) and (3) tropical anhidrotic asthenia (Ladell's heat exhaustion, type II). Heat cramps is not included as a separate entity because it receives no special discussion in this paper. The disorders are analyzed in table 2.

It will be useful to discriminate between the types of anhidrosis which occur in cases of heat disease. I suggest, for reasons already given, that there are two distinct types which may presumably

TABLE 2.—*Typical Features of the Four Main Heat Disorders (When Seen in Pure Form)*

	Coma	Average Body Temperature	Onset of Associated Anhidrosis	Dry Areas	Miliarial and Anhidrotic Rashes	Urine	Cause
Heat Hyperpyrexia (heat or sun stroke)	Present; may be preceded by stupor, mental excitement, twitchings or convulsions	Over 107° F. (41.7° C.) (rectal)	In pure form, sudden (a matter of hours or at most a day or two beforehand)	Whole of body	Not essential; causal relationship likely when rashes are diffuse	Polyuria in early stages, helpful as a warning sign (chlorides present)	Central failure of heat-regulating mechanism due to stress of accommodating to high external temperatures?; sweat glands produce no sweat
Classic heat exhaustion (type I of Ladell and others) <sup>1</sup>	Only syncope; coma rare unless subject at the point of death	100.6° F. (38.1° C.) (rectal)	Anhidrosis not a typical feature		Not essential, but these rashes may be present coincidentally; when present must modify the physiologic and clinical picture	Oliguria (chlorides diminished or absent)	Dehydration because of a sodium chloride deficit within body. deficit being due to an excess of loss in sweat over intake; fluid cannot be retained in absence of sufficient salt—thus "salt deficiency dehydration of extracellular type"
Heat cramps		Not altered in uncomplicated cases	Anhidrosis not a typical feature		(Above comment applies)	Chlorides diminished or absent; (change in volume not essential)	Simple sodium chloride deficiency, not necessarily with dehydration, due to low sodium chloride concentration in body fluids
Tropical anhidrotic asthenia (heat exhaustion, type II, of Ladell and others) <sup>2</sup>	No coma; occasional dimness of vision on exertion; occasional fainting	100.9° F. (38.3° C.) rectally as found by Ladell and others; 100.0° F. (37.8° C.) orally in the present study	At least a few days and usually one or more weeks before	Clothed areas only	One or other or both types of rash always present and severe when looked for after exertion	Polyuria (chlorides present)	Diminished physiologic adaptation to heat due to an obstructive, peripheral form of anhidrosis caused by miliaria; sweat glands still produce a suppressed secretion, which escapes into skin, causing the lesions

Chief authorities consulted were Ladell, Waterlow and Hudson<sup>3</sup>; Taylor, Henschel, Mickelsen and Keys<sup>4</sup>; Nadal, J. W.; Pedersen, S. and Maddock, W. G.: A Comparison Between Dehydration From Salt Loss and Water Deprivation, *J. Clin. Investigation* 20: 691 (Nov.) 1941; and Marriott, H. L.: Water and Salt Depletion, *Brit. M. J.* 1:245 (Feb. 15), 1:285 (March 8) and 1:328 (March 15) 1947.

Mixed states in heat disease are the rule. Temperatures over 103°F. usually indicate heat hyperpyrexia. Not included in the table are (1) simple heat syncope (fainting) and (2) dehydration due to simple water deficiency.

be intermingled. The anhidrosis of heat hyperpyrexia and perhaps of "threatening" heat hyperpyrexia is usually thought to be of central origin—an intrinsic failure or paralysis of the heat-regulating centers.<sup>48</sup> Consequently, it is suggested that in heat hyperpyrexia the sweat glands receive no stimuli to secrete and therefore produce no sweat. The second is the extrinsic or peripheral obstructive type, namely, tropical (post-miliarial) anhidrosis, in which, by contrast, the glands are active but the sweat they produce cannot reach the cutaneous surface; it is reabsorbed as a suppressed secretion from the dermis.<sup>7</sup> The distinction between the two types is believed to be fundamental.

In Ladell's experience, patients with heat hyperpyrexia stated that sweating ceased suddenly over the entire body from half an hour to three hours before general symptoms began. With recovery, recurrence of sweating was just as rapid. Most accounts, such as that of Hearne,<sup>50</sup> agree on the evanescence of this type of anhidrosis, and in this respect the disease differs strikingly from anhidrotic asthenia. Other characteristic features of heat hyperpyrexia are the stupor and the final coma, the extremely high body temperature and, in many cases, diminished or absent knee jerks. During the stage of incipient heat stroke the warning symptoms which may be present<sup>51</sup> are giddiness, nausea, headache, dyspnea and, above all, generalized anhidrosis and polyuria. It will be noted that all these symptoms, except nausea, are prominent in anhidrotic asthenia. The polyuria, like the casual anhidrosis, comes on more acutely in heat stroke.

Ladell and others agree with the almost universally held opinion that in heat hyperpyrexia there is a true failure of the sweating and heat-regulating mechanisms and that the failure probably originates in the central nervous system.

As regards classic heat exhaustion, the Iraq team pointed out that it occurs chiefly in the hottest weather when the requirements of salt and water are at their maximum. The chief clinical features distinguishing it from anhidrotic asthenia are the severe and constant collapse, with pale skin, low pulse pressure (in 35 per cent of cases), cramps (70 per cent), vomiting and dehydration (50 per cent), oliguria and diminished or absent urinary chloride (73 per cent). The most striking distinction

50. Hearne, K. G.: Hyperpyrexial Heat Stroke: A Mesopotamian Experience with Some Aetiological Views and a Method of Prevention Resulting Therefrom, *M. J. Australia* 1:226 (Feb. 13) 1932.

51. Lee,<sup>20</sup> p. 52.

52. Although most writers agree that anhidrosis is not a significant element of classic heat exhaustion, G. H. Collings, L. A. Shoudy and F. E. Shaffer (*The Clinical Aspects of Heat Diseases*, *Indust. Med.* 12:728 [Nov.] 1943) described it as occurring in 26 per cent of a group of patients with exhaustion and cramps. The probability that this proportion may have been in a state of "threatened" heat hyperpyrexia does not seem to have been fully excluded. Neither were the occurrence and the anhidrotic effect of miliaria taken into account.

is the profuse sweating from the skin as a whole.<sup>52</sup> Etiologically, classic exhaustion is regarded by Ladell and others as a manifestation of dehydration secondary to a deficiency of sodium chloride within the body fluids. Peripheral circulatory failure is an important element in the final clinical picture.

It is noteworthy that the internal temperature is not a reliable guide in discriminating between anhidrotic asthenia and heat exhaustion, as in both it is moderately raised. Similarly, headache, giddiness and anorexia may be present in both. On the other hand, the episodes of anhidrotic asthenia are usually more closely associated with exertion, and the symptoms and signs are not as a rule prolonged to any great degree into the postexertional period. Syncope on standing (associated with a rapid, feeble pulse and falling blood pressure), which Ladell and others stress as being so notable in heat exhaustion (73 per cent of cases), is not a prominent feature of anhidrotic asthenia. In the latter, syncope is not common, and, in my experience, is usually precipitated by exercise more strenuous than that of mere standing. Heat exhaustion is curable in a few hours by the use of isotonic sodium chloride solution, and anhidrotic asthenia is not; in cases of the latter an excess of water and salt may possibly be more embarrassing than a deficiency in so far as one of the normal excretory channels (the skin) is largely interrupted.

Although the three listed diseases may occur in a pure form in the dry zones, the Iraq team remarked that the particular clinical picture is frequently complicated by the presence in individual cases of elements of two or more of the syndromes. That this should be so can readily be understood. For if, as is believed, a relatively normal person with previously good sweat function can contract heat hyperpyrexia, it seems only reasonable to postulate that a subject with anhidrosis due to miliaria is, on that account, in even greater danger. Such an association is suggested by Ladell's patients with heat hyperpyrexia, all of whom had some degree of prickly heat on their admission to the hospital, which was, however, "not severe." I would suggest, on the basis of their own remark that only 40 per cent of their subjects with frank anhidrotic asthenia had a dry skin, that Ladell and his co-workers were inclined to underrate the severity of prickly heat in respect to its anhidrotic effect. A relationship between the two diseases is further indicated by one of their cases in which a patient with anhidrotic asthenia had a temperature of 105 F. (40.6 C.), a degree of pyrexia which is not expected in the uncomplicated form of the disease. It is also supported by Wolkin's case 6, in which the extremely rapid onset and disappearance of anhidrosis (apparently complete) suggested the complication of at least some central failure of sweating. It can be presumed that this rather atypical case was included in the series because there was a diffuse anhidrotic rash; in other words, features of both syndromes were seem-

ingly present. Again, Ferris, Blankenhorn, Robinson and Cullen,<sup>53</sup> in a study of 44 patients with heat stroke in the United States of America, found that more than half had, besides a dry skin, a "characteristic maculo-papular skin rash present on the body, being most marked over the chest, abdomen and back. This eruption was fiery red in color and in many areas purpuric." What was this rash if not miliaria complicated by the purpura<sup>54</sup> of heat stroke? Moreover, Morton<sup>55</sup> spoke of a hot dry roughened skin in heat stroke.

It is therefore believed that subjects with miliaria, tropical anhidrosis and anhidrotic asthenia are not immune to heat stroke, and indeed there appears to be good reason to maintain that, owing to their diminished heat tolerance, they are more susceptible than persons who sweat normally. Is it not probable that the compensatory hyperactivity of such glands as escape miliaria may promote the fatigue type of failure as described by Gerking and Robinson?<sup>56</sup> If, as seems likely, further work should prove these views to be correct, miliaria will be credited with a far more vicious status than has hitherto been the case.

It should be pointed out that if heat hyperpyrexia develops in a person with tropical anhidrosis, anhidrotic asthenia or even acute miliaria the associated central paralysis of the sweat mechanism theoretically would lead to the disappearance or at least the amelioration of the characteristic rashes of the conditions, for, as has been shown elsewhere,<sup>7</sup> these rashes owe their origin and continuance to escape of sweat into the tissues of the skin. Therefore, in a case of heat stroke the true state of the skin cannot be correctly estimated until the heat-regulating mechanism recommences its function. The best index of the resumption of the intrinsic activity of the sweat mechanism would be afforded by facial sweating. It can be further presumed that when heat stroke develops in a person with anhidrotic asthenia all areas which were previously sweating, such as the face, become dry. As heat stroke was not encountered during the present study, the suggestions could not be put to a test.

It is also possible that patients with classic heat exhaustion may show some manifestations of tropical (postmiliarial) anhidrosis. For instance, it appears from the account of Ladell and his co-workers that

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53. Ferris, E. B.; Blankenhorn, M. A.; Robinson, H. W., and Cullen, G. E.: Heat Stroke: Clinical and Chemical Observations on Forty-Four Cases, *J. Clin. Investigation* 17:249 (May) 1938.

54. Wright, D. O.; Reppert, L. B., and Cuttino, J. T.: Purpuric Manifestations of Heat Stroke, *Arch. Int. Med.* 77:27 (Jan.) 1946.

55. Morton, T. C.: Heat Effects in British Service Personnel in Iraq, *Tr. Roy. Soc. Trop. Med. & Hyg.* 37:347 (May) 1944.

56. This probability is not incompatible with my opinion that in the humid zones a fatigue type of anhidrosis is not responsible for any part of the clinical picture of either tropical (postmiliarial) anhidrosis or anhidrotic asthenia.

some of their subjects with classic heat exhaustion had symptoms which truly belong to tropical anhidrosis, namely, a history of "defective sweating" (13 per cent of cases), "desquamating prickly heat" (7 per cent) and skins classified as "dry" (5 per cent).<sup>57</sup> Conversely, 4 per cent of their patients with anhidrotic asthenia had cramps and vomiting, features normally part of heat exhaustion. These observations certainly favor the idea that mixed states of heat exhaustion and tropical anhidrosis occur.

Nevertheless, providing present etiologic conceptions are correct, fully developed heat exhaustion and fully developed anhidrotic asthenia are perhaps mutually exclusive in so far as a patient with more than a moderate degree of tropical anhidrosis is probably unable to lose enough sodium chloride through the skin to be in danger of heat exhaustion. It is therefore predicted that patients with heat exhaustion are unlikely to show more than a mild degree of tropical (postmiliarial) anhidrosis. Conversely, patients with anhidrotic asthenia are not prone to the salt and water deficiencies of heat exhaustion; in particular, cramps, vomiting, oliguria or achlouria are not to be expected. That 4 per cent of Ladell's patients with anhidrotic asthenia did in fact have cramps and vomiting cannot be easily explained on present hypotheses; perhaps in these instances vomiting, which is typically absent or inconspicuous, led to an excessive loss of chloride in the vomitus. Despite all that has been said in this paragraph, there is still scope for an etiologic connection between tropical anhidrosis and classic heat exhaustion. It has already been noted that tropical anhidrosis probably precipitates a rise in the sweat chloride concentration or is associated with it. Should the rise in chloride concentration relatively outstrip the fall in sweat production, then the total loss of chloride from the body could clearly increase. This possible effect of miliaria is well worth study.

Because of its intermittent nature, anhidrotic asthenia is prone to be mistaken for a psychiatric disorder. Confusion arises since those affected say that their inability to work is confined to the middle of the day. The morning sick parade held by the services does not facilitate diagnosis, for at that time the subjects feel well and may show to an unwary eye no evidence of the anhidrosis and rash. However, they give a typical history which, if not conclusive, is at least suggestive. There should be no difficulty when the persons are observed at work. If the cutaneous changes are ignored, simple indolence and the "effort syndrome" (Lewis) are other possible sources of confusion.

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57. From their account, it is unlikely that "threatened" heat stroke could have been responsible for the "defective sweating" and "dry skin" seen in these instances.



## INCIDENCE OF MILIARIA AND TROPICAL ANHIDROSIS IN THE FIELD

Inspection of units reveals that severe anhidrotic asthenia, mild anhidrotic asthenia and simple tropical (postmiliarial) anhidrosis are increasingly prevalent in that order. In carrying out such survey work, it is necessary to examine all subjects immediately after exertion. Further, in the estimation of cutaneous changes, it is important to be guided more by the profusion of the various miliarial and anhidrotic lesions than by the presence or absence of patches of complete dryness. My experience with troops was that 35 to 70 per cent had the characteristic cutaneous changes to at least a "moderately severe" degree, the basis for these estimates having been the "severe" involvement of the skin in frank anhidrotic asthenia. The more active units showed the greater incidence. It was thought unwise to resort to the direct elicitation of symptoms on these routine inspections of units; still, it was hard to avoid the conclusion that a large proportion of the men would have been fitter without their anhidrosis. It is unfortunate that the severity of an anhidrosis cannot be easily measured quantitatively; neither can the associated loss of adaptation. In general, one can only be guided by previous knowledge of asthenic patients.

The incidence of moderately severe obstructive anhidrosis (35 to 70 per cent) probably depends on the incidence of miliaria as it varies from one unit to another.<sup>58</sup> As regards general symptoms, I have made the broad tentative suggestion<sup>7</sup> that when half the sweat pores on the covered parts are blocked, there is probably some loss of adaptation and that when two thirds or more are affected, the loss of adaptation is likely to be severe. Precise measurements of the amount and the chloride content of the sweat produced in anhidrotic states of varying intensity would be of much interest.

## TERMINOLOGY

The thermal disorder which may follow miliaria is specific enough to merit a name. From the point of view of time of publication, "thermogenic anhidrosis" has priority by a few months. Yet this name is not entirely suitable, for while it has the advantage of stressing the significant role of the anhidrosis, it is defective in the use of the qualification "thermogenic." As a result, the meaning of the combined term is not clear; if it is intended to convey the impression that the high external

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58. In the Merauke climate, Kendall<sup>13</sup> found that 91 per cent of the men in his unit suffered from miliaria at one time or another during a period of ten months. M. B. Sulzberger and L. O. Emik (*Studies on Prickly Heat: I. Clinical and Statistical Findings*, *J. Invest. Dermatol.* 7:53 [Feb.] 1946) found an incidence of 66 per cent during a period of seven months on Guam.

temperature produces the anhidrosis it is open to criticism because present knowledge is against such a relationship in this disease. At best a connection is remote and exists through the mediation of miliaria. "Thermogenic anhidrosis" is also unsatisfactory if it is intended to convey the idea that the anhidrosis produces a dramatic rise in the body temperature. The rise in temperature is almost always slight in the uncomplicated form of the disease; the exhaustion and the other asthenic features are far more noteworthy.

Ladell and others showed reticence in their choice of the term "heat exhaustion, type II." Their paper gives the impression that although they were convinced of the basic role of the anhidrosis they were not prepared to sponsor the association by giving it a name. They once used the term "anhidrotic heat exhaustion," and although this was satisfactory they did not persevere with it. However, as most physicians already have in their minds a concept of classic heat exhaustion, including its cause, it seems a pity to confuse matters now by dividing heat exhaustion into two different clinical and etiologic types, particularly in so far as it is now justifiable to adopt an etiologic name for the "type II."

"Tropical anhidrotic asthenia" appears to get over these difficulties and was chosen after much familiarity with the disease. It is descriptive in that it implies the leading characteristics of the disease, i.e., the anhidrosis, and the combination of asthenic symptoms and signs. Further, the name arose out of the earliest work in the field<sup>6</sup> and has recently been adopted by Sulzberger and others<sup>12</sup> for their contributions.

#### SUMMARY

In their classic paper on the physiologic and clinical responses of man to the desert, Ladell, Waterlow and Hudson<sup>5</sup> ask: "Is severe prickly heat inevitably or usually followed by general symptoms?" The certain answer, which they help to give, is "inevitably, yes." By involving blockage of the sweat pores, miliaria produces anhidrosis and thereby diminishes heat tolerance. The broad inferences of this simple concept need hardly be stressed.

The heat disease produced by miliaria is subtle and shows little of the urgency and danger to life associated with the familiar syndromes. It is distinguished rather by malaise, a distaste for work and excessive fatigue on physical activity. In other words, it is closely bound up with the subtle problem of incipient loss of acclimatization.

The several accounts from both the wet and the dry zones are re-

markably similar. After arrival in the tropics and a few months of health comes the provoking attack of miliaria. The attack may or may not be severe. After a further but shorter latent period, the patient commences to suffer from asthenic symptoms, exhaustion, headache, dyspnea and giddiness, when working in the heat. When seen after exercise he shows not only gross cardiorespiratory distress but also an anhidrosis on the covered areas and a characteristic anhidrotic (goose-flesh-like) rash. The disease, which has been named tropical anhidrotic asthenia, lasts some weeks and may then pass away as gradually as it came on.

As regards differences between the various accounts, one team's suggestion that the anhidrosis is preceded by a period of generalized, excessive sweating is not supported by the results of close analysis. However, the observation that all unblocked sweat glands hypersecrete during the course of the disease is accepted by all. Another team does not record seeing the anhidrotic rash. This disparity is probably explicable on the basis of terms rather than of objective distinctions.

Why a subject with anhidrosis should suffer from symptoms when exposed to heat poses tantalizing problems. Many factors probably play a part, and different authors stress them in varying degree. One observation which has to be taken into account is that the body temperature typically does not rise as high as might be expected. This is significant, for at least one group of writers emphasizes the stimulating effect of increased blood temperature on the respiratory center. Another team favors the idea that the symptoms and signs arise because of an alkalosis which results from a panting type of compensatory hyperpnea. This hypothesis lacks sufficient clinical evidence, and the available chemical data are merely consistent and not positively supportive. On the other hand, it is proposed in the present paper that while some truth may rest in all these hypotheses most of the clinical response to exercise is probably accounted for by a temporary circulatory failure of peripheral type. The following postulates are reached in a review of the classic heat disorders in the light of present knowledge of anhidrotic asthenia:

1. There are two distinct types of anhidrosis encountered in the tropics. One is associated with heat hyperpyrexia and is thought to be due to an intrinsic, central failure of the sweat mechanism. The other is the peripheral obstructive type associated with miliaria and its sequelae, tropical (postmiliarial) anhidrosis and anhidrotic asthenia.

2. Because it lowers heat tolerance, miliaria probably predisposes toward heat hyperpyrexia. The sequence of events may well be as

follows: miliaria, compensatory hyperactivity of unaffected sweat glands, fatigue or failure of the sweat mechanism and heat hyperpyrexia.

3. By causing a rise in the chloride concentration of sweat, miliaria and its sequelae may, under specified conditions, predispose toward classic heat exhaustion.

4. The presence of any anhidrosis due to miliaria must modify the clinical and pathologic pictures of the classic heat disorders.

## NEEDLE BIOPSY OF THE LIVER

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IT HAS been apparent for years that some aid must be found in making an early diagnosis of diseases of the liver, especially when there is minimal or moderate functional impairment. Employment of needle biopsy of the liver has been useful in this regard, and evidence is accumulating which indicates the value of this procedure.

Through the use of the biopsy needle, new light has been shed on some of the problems which have always been difficult to solve diagnostically. This is well illustrated in instances of prolonged jaundice, in which it is imperative to determine whether the cause is intrahepatic or extrahepatic, in order to institute the proper treatment. Another problem frequently encountered is that of portal cirrhosis, the manifestations of which may be overlooked or difficult to evaluate, especially in early cases or in the presence of disease of the heart and/or kidneys. Similarly, the role of enlargement of the liver secondary to a systemic disease, such as diabetes mellitus, thyrotoxicosis, amyloidosis or hemochromatosis, is difficult to determine. Patients suffering from carcinoma of the liver, metastatic or primary, are often subjected to laparotomy because the condition was undiagnosed beforehand.

Experience with one hundred and eleven biopsies of the liver in 100 patients has led us to analyze our results in order to determine the diagnostic value of this measure, to estimate the percentage in which a specimen satisfactory for histologic study may be obtained and to emphasize the indications, contraindications and complications associated with biopsy of the liver.

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## REVIEW OF THE LITERATURE

The first recorded biopsy of the liver was performed in 1895 by Lucatello,<sup>1</sup> although puncture of the liver for therapeutic purposes in cases of abscess and hydatid disease had been reported by Biett<sup>2</sup> and Roberts (performed by Stanley<sup>3</sup>) in 1833, Hammond<sup>4</sup> in 1878 and Sims<sup>5</sup> in 1879. Twelve years after Lucatello's original work, Schupfer<sup>6</sup> reported a series of cases of biopsy of the liver. These investigators used a technic consisting of the introduction of a small bore needle into the liver, followed by aspiration of a few fragments of hepatic tissue and blood, which were smeared on a slide, stained and examined. Although this method entails relatively little risk and is said to enable frequent diagnoses, it does not permit a study of architecture and stroma. Frola<sup>7</sup> reviewed the reports of aspiration biopsy of the liver in a monograph published in 1935 and reported 66 cases of his own. Examination of his photomicrographs reveals a few particles of hepatic tissue and blood cells, which demonstrates the limited value of this technic. Despite these handicaps, this method has retained popularity in Europe, as evidenced by a number of reports in recent years.<sup>8</sup>

In 1923, Bingle and Olivet developed a technic which enabled them to obtain a small specimen of hepatic tissue which was satisfactory for the preparation of paraffin sections. Bingel<sup>9</sup> reported 100 cases, with

1. Lucatello, L.: Sulla puntura del fegato a scopo diagnostico, *Lavori d. Cong. di med. int.* **6**:327-329, 1895.

2. Biett: Hydatides du foie, avec développement considérable de cet organe: Ponction explorative; incision; sortie d'une grande quantité d'acéphalocystes; guérison, *Gaz. d. hôp.* **7**:383, 1833.

3. Stanley: Cases at St. Bartholomew's Hospital, *Lancet* **2**:189-190 (Oct. 26) 1833.

4. Hammond, W. A.: Some Points in the Pathology and Treatment of Hepatic Abscesses, *St. Louis M. & S. J.* **35**:72-76, 1878.

5. Sims, J. M.: Diagnosis of Abscess of the Liver by Symptoms of Cerebral Hyperaemia, with Some Remarks on Treatment of Hepatic Abscess by Aspiration, *Tr. M. Soc. Virginia* **3**:106-111, 1879.

6. Schupfer, F.: De la possibilité de faire intra vitam un diagnostic histopathologique précis des maladies du foie et de la rate, *Semaine méd.* **27**:229, 1907.

7. Frola, E.: Il puntato epatico nella diagnosi delle malattie del fegato, Rome, Luigi Pozzi, 1935.

8. Huard, P.; Meyer, M. J., and Joyeux, B.: La ponction biopsie du foie et son utilité dans le diagnostic des affections hépatiques, *Ann. d'anat. path.* **12**:1118-1124 (Dec.) 1935. Fiessinger, N., and Laur, C. M.: L'hépatogramme en clinique courante, in particulier dans le diagnostic du cancer du foie, *Sang* **12**:102-106, 1938. Weil, P. E.; Isch-Wall, P., and Perles, S.: La ponction du foie dans l'ictère hémolytique, la cirrhose pigmentaire, le cancer mélanique, *ibid.* **12**:97-102, 1938. Hatieganu, I.; Sparchez, T.; Radu, P., and Macavie, I.: Der Wert der Leberpunktion in der Diagnose der verschiedenen Lebererkrankungen, *Wien. klin. Wchnschr.* **56**:21 (Jan. 15) 1943.

9. Bingel, A.: Ueber die Parenchympunktion der Leber, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **35**:210-212, 1923.

2 deaths due to hemorrhage, and Olivet<sup>10</sup> in 1926 evidently extended the series, reporting 140 cases, with an additional death due to peritonitis. A modification of their technic, which has been widely used since, was developed by Iversen and Roholm<sup>11</sup> in 1939. These investigators used a cannula 18 cm. long and 2 mm. wide and a pointed stylet. After antiseptic cleansing and anesthesia, this needle is introduced into the ninth intercostal space in the posterior axillary line and inserted into the liver, after passing through the pleural space and the diaphragm, while the patient holds his breath in expiration. The stylet is withdrawn and a record syringe (10 cc.) attached to the cannula. Suction is then applied and the needle forced 1 to 2 cm. farther into the liver while the syringe is rotated. The cannula is then quickly withdrawn and yields a specimen satisfactory for microscopic examination. They reported one hundred and sixty biopsies on 114 patients with this method, with a successful result in 22.5 per cent. Two patients evidenced signs of intraperitoneal hemorrhage, which at autopsy was not thought to have caused death. A further report of eleven biopsies, without complications, of 10 patients, performed in a study of hepatitis, was presented by Roholm and Krarup<sup>12</sup> in 1940. Dible, McMichael and Sherlock<sup>13</sup> in England made a study of epidemic hepatitis, arsenotherapy jaundice and serum jaundice during World War II, using the method of Iversen and Roholm. They reported one hundred and twenty-six punctures of the liver, following which 2 patients had nonfatal hemorrhage, 1 patient had hemorrhage but died of acute necrosis of the liver and 1 patient died of necrosis of the liver and rectal carcinoma and was observed to have blood-stained ascitic fluid at autopsy. This series was apparently extended by Sherlock<sup>14</sup> in 1945 in a report of one hundred and thirty-eight additional biopsies, using the same technic but with a longer and narrower needle. Approximately 6 per cent failure was recorded for the two hundred and

10. Olivet, J.: Diagnostic Puncture of Parenchyma of Liver, *Med. Klin.* **22**: 1440-1443 (Sept. 17) 1926.

11. Iversen, P., and Roholm, K.: On Aspiration Biopsy of Liver, with Remarks on Its Diagnostic Significance, *Acta med. Scandinav.* **102**:1-16, 1939. Roholm, K., and Iversen, P.: Changes in Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, *Acta path. et microbiol. Scandinav.* **16**:427-442, 1939.

12. Roholm, K., and Krarup, N. B.: Die Histopathologie der Leber bei sog. Salvarsanikterus, mittels Aspirationsbiopsie untersucht, *Arch. f. Dermat. u. Syph.* **181**:521-523, 1940.

13. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, *Lancet* **2**:402-408 (Oct. 2) 1943.

14. Sherlock, S.: Aspiration Liver Biopsy: Technique and Diagnostic Application, *Lancet* **2**:397-401 (Sept. 29) 1945.

sixty-four biopsies, with no additional complications or fatalities. These authors emphasized that biopsy of the liver should not be performed unless adequate facilities for blood transfusion are available, in the event of hemorrhage. They also stated that the risk of hemorrhage is greatest in severely jaundiced patients, especially if the jaundice is due to acute parenchymatous hepatic disease, and added that they had never observed evidence of hemorrhage in nonjaundiced patients. Van Beek and Haex<sup>15</sup> reported 100 cases of aspiration biopsy of the liver in cases of infectious mononucleosis and benign sarcoid.

Laparoscopic control of biopsy of the liver was reported in one hundred and twenty-three instances by Kalk, Bruhl and Sieke<sup>16</sup> in 1943, with no complications. This method is undoubtedly safer than biopsy with an external approach alone, but it involves the use of the operating room and is time consuming.

In the first report of biopsy of the liver in the United States in 1939, Baron<sup>17</sup> recorded forty-eight aspiration biopsies in 35 patients, several of which were performed intercostally. This technic was abandoned in later cases, because of the potential dangers associated with its use, and an anterior subcostal approach was used. One fatal hemorrhage occurred in this series. Chiray, Fiessinger and Roux<sup>18</sup> also used the anterior subcostal approach in 41 cases reported, in which there was 20 per cent failure. These authors had no untoward results and ascribed this to their having penetrated the liver only to a depth of 3 cm., thus avoiding the large blood vessels. Introduction of the biopsy needle at the apex of the angle between the xiphisternum and the right costal margin was reported by Gillman and Gillman<sup>19</sup> in 1945 in a series of five hundred biopsies of the liver.

A special needle primarily intended for biopsy of tumors was first described by Silverman<sup>20</sup> in 1938. The use of this instrument for

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15. Van Beek, C., and Haex, A.: Aspiration-Biopsy of Liver in Mononucleosis Infectiosa and in Besnier-Boeck-Schaumann's Disease, *Acta med. Scandinav.* **113**:125-134, 1943.

16. Kalk, H.; Bruhl, W., and Sieke, W.: Deliberate Liver Puncture, *Deutsche med. Wchnschr.* **69**:679-712 (Oct. 1) 1943; abstracted, *J.A.M.A.* **128**:157 (May 12) 1945.

17. Baron, E.: Aspirations for Removal of Biopsy Material from the Liver, *Arch. Int. Med.* **63**:276-289 (Feb.) 1939.

18. Chiray, M.; Fiessinger, N., and Roux, M.: La ponction-biopsie du foie, *Presse méd.* **49**:785-788 (July 22) 1941.

19. Gillman, T., and Gillman, J.: A Modified Liver Aspiration Biopsy Apparatus and Technique, with Special Reference to Its Clinical Applications as Assessed by Five Hundred Biopsies, *South African J. M. Sc.* **10**:53-56 (June) 1945.

20. Silvermann, I.: A New Biopsy Needle, *Am. J. Surg.* **40**:671-672 (June) 1938.



biopsy of the liver was recorded in a report of 14 cases in a series of unstated number by Tripoli and Fader<sup>21</sup> in 1941. They recommended the anterior subcostal approach, just to the right of the rectus muscle, where the abdominal wall is thin, and confined their biopsies to patients in whom the liver was palpable. Using the method described by Tripoli and Fader, Hoffbauer<sup>22</sup> in 1945 reported sixty-five biopsies, with no serious hemorrhage. Twenty of these biopsies were performed under peritoneoscopic control, with a modified Vim-Silverman needle, 18 cm. in length. Most of these cases are apparently included in a report by Hoffbauer, Evans and Watson,<sup>23</sup> published in 1945, on a study of cirrhosis of the liver and the correlation of tests of hepatic function with biopsy of the liver. They reported 85 cases, in 15 of which failure occurred (18 per cent) and in 20 of which the technic was carried out in the operating room under peritoneoscopic control. The Vim-Silverman needle was used in all instances, and one severe nonfatal hemorrhage occurred. The authors were not able to correlate the results of studies of hepatic function with the histologic changes in the biopsy specimen of the liver. In 1946, Davis, Scott and Lund<sup>24</sup> reported seventy-nine biopsies, with 86 per cent success, using several instruments, including a large bore needle, the Vim-Silverman needle and the Roth-Turkel needle.<sup>25</sup> There were no fatalities. In commenting on the use of the Roth-Turkel needle, the authors pointed out that while it is larger and yields larger specimens without compression of tissue, it is more difficult to control than the Vim-Silverman needle. Popper, Franklin, Steigmann and Kozoll<sup>26</sup> reported a study in 1946 in which biopsies had been performed on 85 patients. They stated that they were able to correlate accurately the results of some studies of hepatic function and certain pathologic changes, as revealed by histologic changes in the biopsy specimen.

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21. Tripoli, C. J., and Fader, D. E.: Differential Diagnosis of Certain Diseases of Liver by Means of Punch Biopsy, *Am. J. Clin. Path.* **11**:516-527 (June) 1941.

22. Hoffbauer, F. W.: Needle Biopsy of the Liver, *Journal-Lancet* **65**:246-248 (July) 1945.

23. Hoffbauer, F. W.; Evans, G. T., and Watson, C. J.: Cirrhosis of Liver Presenting Clinical Features of Xanthomatous Biliary Cirrhosis but with Confirmation at Autopsy (Follow-Up of Case Reported Previously), *M. Clin. North America* **29**:1054-1055 (July) 1945.

24. Davis, W. D.; Scott, R. W., and Lund, H. Z.: Needle Biopsy of the Liver, *Am. J. M. Sc.* **212**:449-461 (Oct.) 1946.

25. Roth, A. A., and Turkel, H.: Technique of Prostatic Biopsy, *J. Urol.* **51**:66-68 (Jan.) 1944.

26. Popper, H.; Franklin, M.; Steigmann, F., and Kozoll, D. D.: Relation Between Structural and Functional Alterations of the Liver, *Proc. Central Soc. Clin. Research* **19**:11-12, 1946.

## METHOD AND MATERIALS

From August 1945 to February 1947, we performed one hundred and eleven biopsies of the liver of 100 patients.<sup>27</sup> Of these, 63 were male and 37 were female; 93 were white, and 7 were Negro. The ages ranged from 29 to 79 years. The Vim-Silverman needle was used in all instances, and one hundred and seven of the biopsies were performed ante mortem. Ninety-seven biopsies (87.4 per cent) were successful, and fourteen biopsies (12.6 per cent) failed in this series, the latter including those in which too little tissue or no tissue was obtained for study. Failure was due principally to lack of experience in use of the technic, as the last fifty-five biopsies performed were successful. A sharp needle is necessary to obtain a satisfactory core of tissue, and we feel that three of our failures may be attributed to not having had the needle sharpened. Other failures were due to livers being palpable less than 2 cm. below the right costal margin and to cystic disease. The technic used is as follows:

The procedure is performed at the bedside, following the administration of 50 to 100 mg. of meperidine hydrochloride to allay apprehension. After the usual preparation of the skin with iodine and alcohol, a sterile drape is placed over the area selected for biopsy. This may be located at any point where the liver is easily palpable: below the right costal margin in the midclavicular line, in the midline below the xiphoid process or in the right flank. If there are any palpable nodules, an attempt is made to enter one of them. From 4 to 6 cc. of 2 per cent procaine hydrochloride is then infiltrated into the skin and subcutaneous tissues down to and including, if possible, the parietal peritoneum. As a rule, the patient will give some sign when the point of the needle reaches the peritoneum, and an additional 0.5 cc. is injected at this point. In approximately two minutes the anesthetic is effective, and a small incision is made in the skin to facilitate passage of the needle. The needle, with the obturator in place, is then inserted through the anesthetized tract and into the liver for 1 to 2 cm., at an angle of approximately 45 degrees. This is done in order to avoid passing the needle completely through a thin right lobe, which might result in injury to the gallbladder or other structure beneath. To be relatively sure that the needle is in the liver, the patient is requested to inspire; if properly placed, the hub of the needle will swing cephalad. The obturator is withdrawn and suction applied by means of a 2 cc. syringe, in order to be sure that an excessively vascular area, a cyst or an abscess has not been entered.

The split biopsy needle is then inserted all the way into the needle in situ, which allows about 2 cm. of the split biopsy needle to extend beyond the end of the outer needle and to grasp the core of hepatic tissue. With the split biopsy needle held firmly in place, the outer needle is then rotated and advanced at the same time until it has reached the end of the inner needle. This will compress the core of tissues between the prongs of the split biopsy needle, and after one complete rotation the two needles are withdrawn simultaneously. The specimen is placed in a small quantity of 10 per cent formaldehyde for twenty-four hours and paraffin sections are made from it. The activities of the patient are not limited because of the procedure, but he is kept in the hospital at least twenty-four hours afterward for observation.

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27. The biopsies were performed at the Milwaukee County General Hospital, Wauwatosa, Wis., and the Veterans Administration Center, Wood, Wis.

The pathologic diagnoses made from the biopsy specimens of the liver are summarized in table 1. Classification of cases of portal cirrhosis into early, moderate and advanced types (fig. 1, 2, 3 and 4) was based on the degree and type of hepatic cell abnormality and the amount of fibrous tissue proliferation seen and is admittedly subjective in a small proportion of the cases. The diagnosis of cardiac cirrhosis (fig. 5) was made on specimens showing the changes of portal cirrhosis plus the dilated central vein. A history of long-standing cardiac disease was also given. The diagnosis of toxic cirrhosis was based also on observations in slides revealing decided increase in cellular infiltration in the periportal areas plus the changes of portal cirrhosis. A report of diagnosis of carcinoma (figs. 6, 7, 8 and 9) described the type of malignant condition as "adenocarcinoma" or "squamous cell carcinoma," but was seldom more specific. In several cases, an attempt was made to suggest the primary site of the malignant condition on the basis of the specimen alone, but this was not uniformly successful. Miscellaneous cases included 3 in which there was normal hepatic tissue and 4 in which there were nonspecific degenerative changes with pigmentation (fig. 10).

TABLE 1.—*Pathologic Diagnosis Made from Biopsy Specimens of the Liver*

<i>Diagnosis</i>	<i>No. of Cases</i>
Portal cirrhosis	
Early .....	14
Moderate .....	10
Advanced .....	23
Biliary cirrhosis .....	4
Toxic cirrhosis .....	3
Cardiac cirrhosis .....	3
Acute hepatitis .....	1
Carcinoma, metastatic (all types) .....	20
Brown degeneration .....	4
Hemochromatosis .....	4
Fatty metamorphosis .....	3
Amyloidosis .....	1
Miscellaneous .....	7

There were no deaths attributable to the biopsy of the liver in this series. Only three minor complications were observed. One was a small hematoma into the abdominal wall at the site of puncture and another a moderately severe hemorrhage noted during the procedure and followed by the development of a tender nodule in the area of puncture about one week after biopsy. This was interpreted as a hematoma either under Glisson's capsule or just outside the hepatic substance. Approximately 25 per cent of the patients complained of pain or vague abdominal discomfort during or shortly after the biopsy. The pain was seldom severe and occurred at the site of puncture or was referred to the chest or left flank. It did not last for more than an hour or two in any case, with the exception of four instances in which pain persisted for three to nine days. In none of these cases was an opportunity to search for underlying pathologic change afforded at autopsy.

The true value of needle biopsy of the liver in diagnosis is determined by a comparison of the results obtained from biopsy and the postmortem observations given in table 2. In addition, we have listed the clinical diagnoses, in order to emphasize the role of biopsy of the liver. Of 100 patients, 36 are known to have died, and autopsy was done on 19 (52.8 per cent) of these. Attempts at biopsy of the liver were unsuccessful in 3 of the autopsied patients. Concerning the remaining 16 cases, in case 5 failure occurred in that the metastatic lesions were missed when the biopsy needle passed within a few millimeters of two tumor nodules. The biopsy of the liver in case 7 confirmed the clinical impression and



Fig. 1.—Early portal cirrhosis of the liver.



Fig. 2.—Moderate portal cirrhosis of the liver.

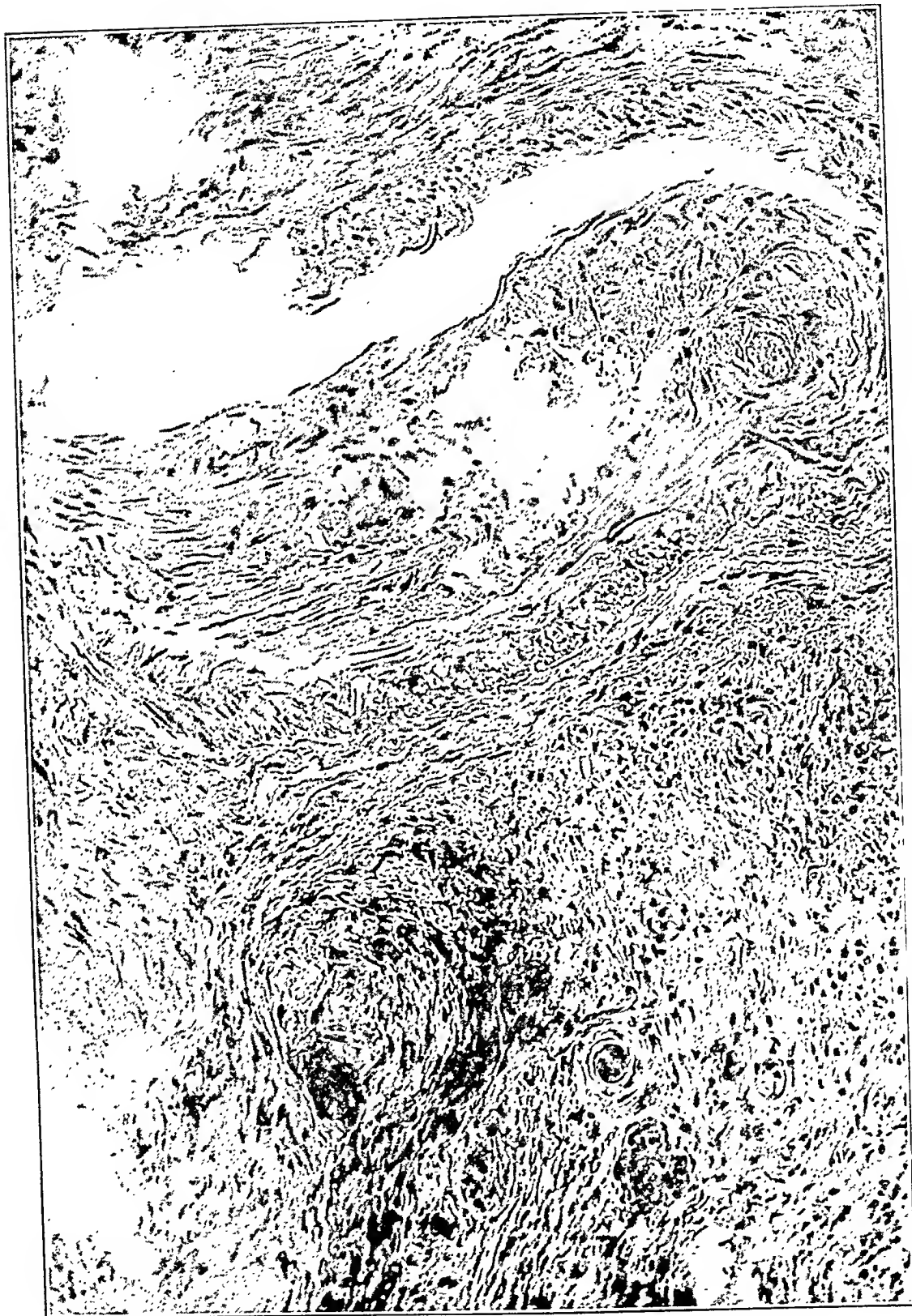


Fig. 3.—Advanced portal cirrhosis of the liver, of toxic origin.



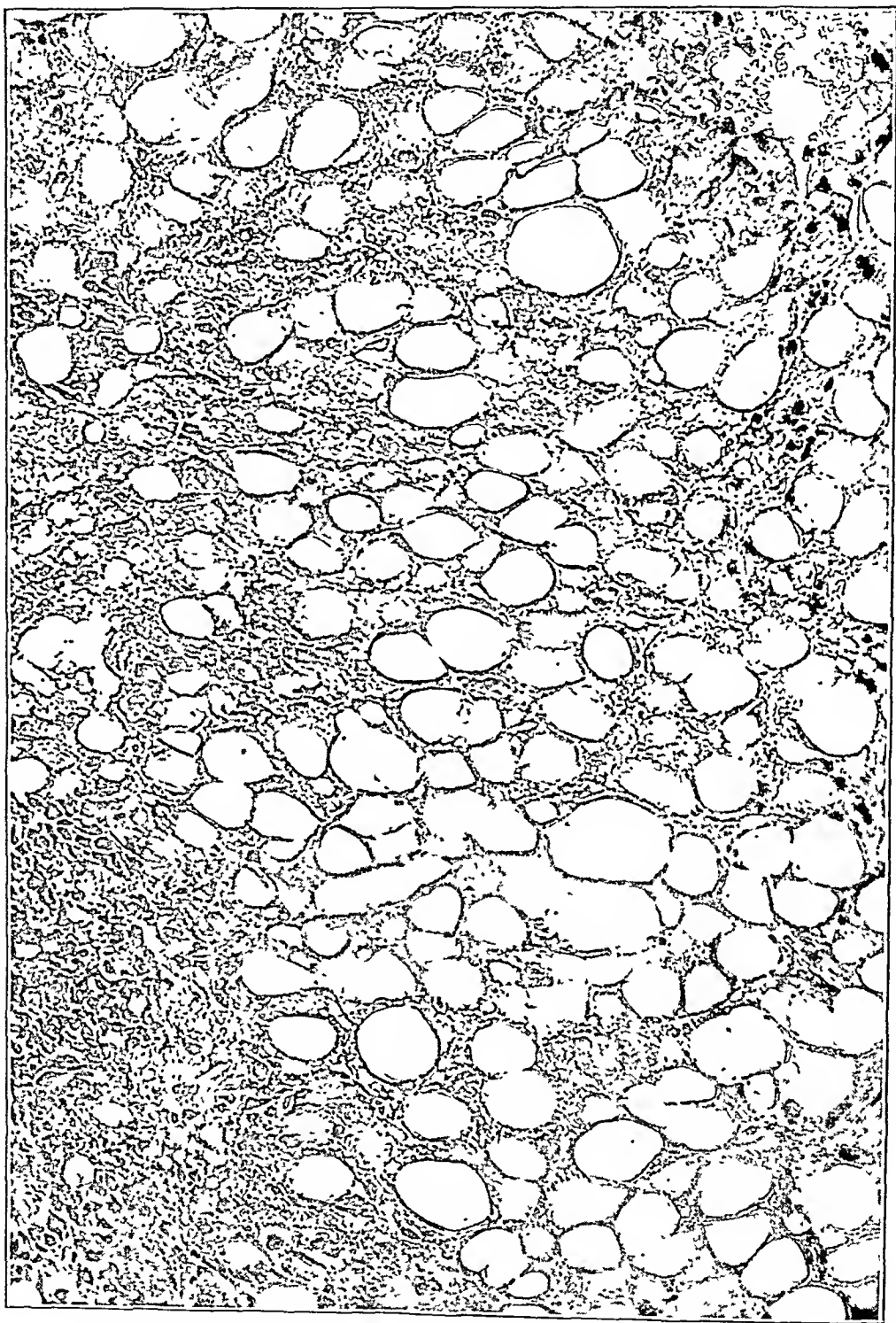


Fig. 4.—Portal cirrhosis of the liver, with decided fatty change.



Fig. 5.—Cardiac cirrhosis.



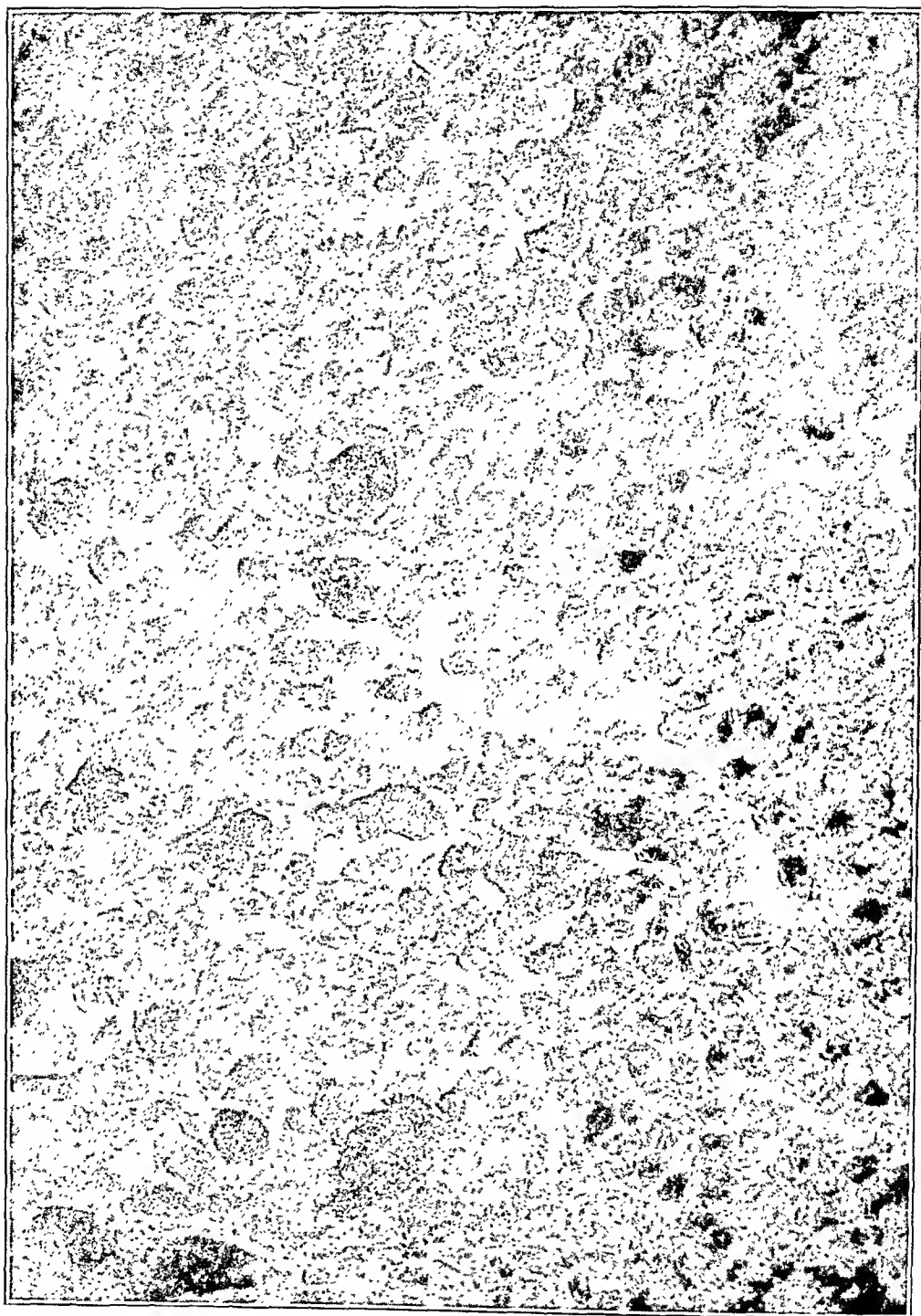


Fig. 6.—Metastatic melanoma of the liver, from a patient with retrobulbar melanoma.



Fig. 7.—Metastatic carcinoma of the liver from the breast.



Fig. 8.—Metastatic carcinoma of the liver from the stomach.

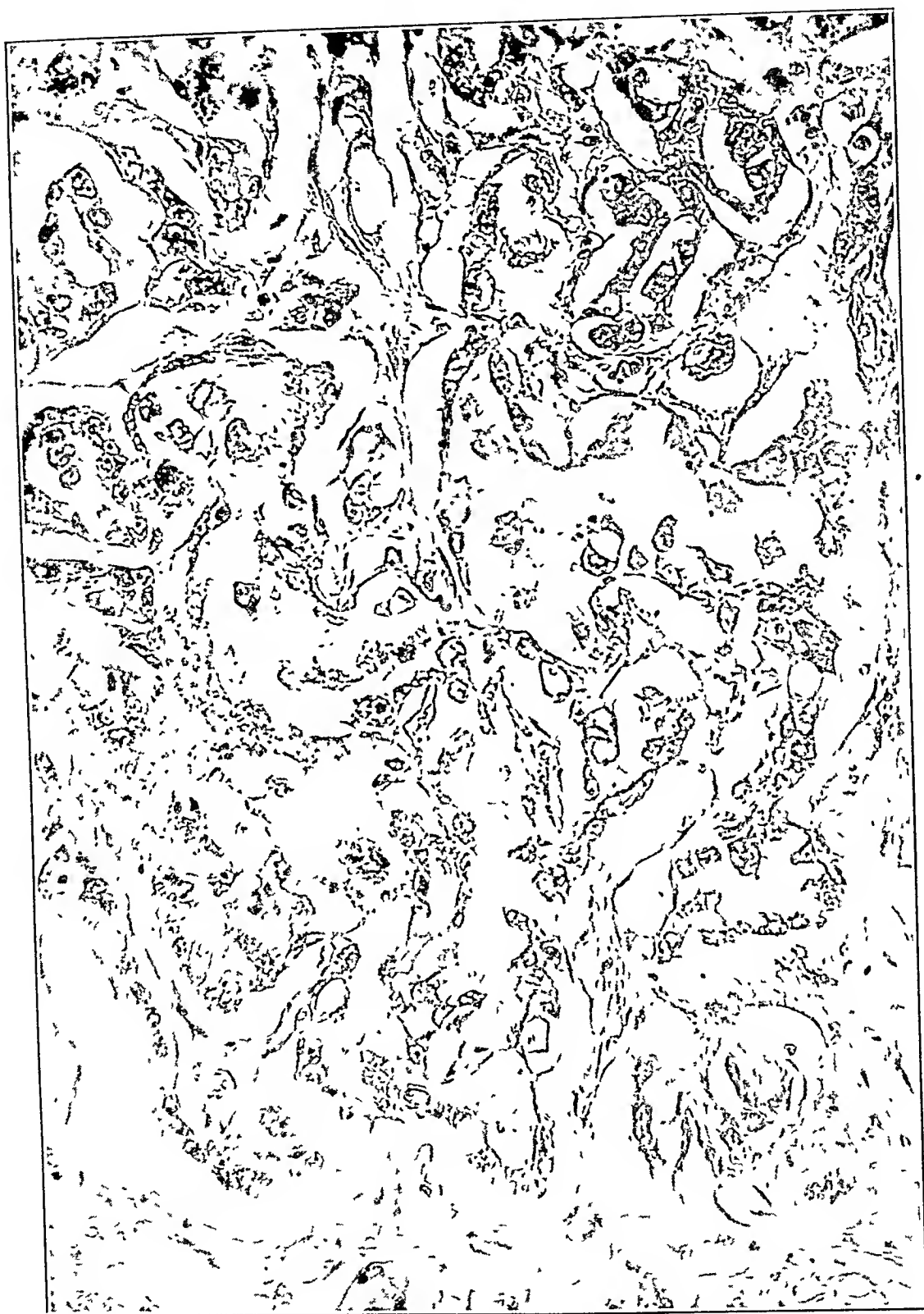


Fig. 9.—High grade metaplastic carcinoma of the liver, simulating squamous cell carcinoma, in a patient with carcinoma of the pancreas.

TABLE 2.—*Correlation of Clinical Diagnoses and Diagnoses from Biopsy of the Liver and Autopsy*

Clinical No.	Clinical Diagnosis	Diagnosis from Biopsy of the Liver	Diagnosis at Autopsy*
3	Extralepatic obstructive jaundice, cause undetermined	Biliary type cirrhosis	Biliary cirrhosis due to carcinoma of the ampulla of Vater
5	Metastatic carcinoma of the liver, primary site undetermined	Normal hepatic tissue	Carcinoma of splenic flexure of the colon with metastasis to the liver
6	Portal cirrhosis	Portal cirrhosis (with fatty change)	Portal cirrhosis with chronic miliary tuberculosis of the lungs, intestines and peritoneum
7	Portal cirrhosis	Portal cirrhosis (early)	Portal cirrhosis and carcinoma of the gallbladder with local metastasis
8	Metastatic carcinoma of the liver, primary site undetermined	Metastatic adenocarcinoma	Carcinoma of the gallbladder with metastasis to the liver
9	Portal cirrhosis	Metastatic adenocarcinoma, suggested primary site is breast	Carcinoma of the breast with metastasis to the liver
10	Metastatic carcinoma of the liver, primary site undetermined	Metastatic adenocarcinoma	Primary carcinoma of the liver
11	Portal cirrhosis	Portal cirrhosis (advanced)	Portal cirrhosis (advanced)
12	Carcinoma of the colon with metastatic to the liver	Metastatic adenocarcinoma, suggested primary site is colon	Carcinoma of the descending colon with metastasis to the liver
13	Portal cirrhosis	Portal cirrhosis (advanced)	Portal cirrhosis (advanced)
15	Metastatic carcinoma of the liver	Metastatic adenocarcinoma, suggested primary site is colon	Carcinoma of prostate with metastasis to liver
16	Metastatic carcinoma of the liver	Metastatic adenocarcinoma	Carcinoma of stomach with metastasis to liver
17	Portal cirrhosis, multiple myeloma, pyelonephritis	Portal cirrhosis (advanced)	Portal cirrhosis (advanced), multiple myeloma, suppurative pyelonephritis
18	Metastatic carcinoma of the liver, primary site undetermined	Infiltrating carcinoma, apparently of squamous cell origin	Carcinoma of pancreas with metastasis to liver
19	Miliary infiltration—both lungs (probably carcinoma)	Hemochromatosis	Hemochromatosis and bronchiectasis

\*Attempts at biopsy of the liver were unsuccessful at autopsy in 3 cases.

demonstrated the pathologic changes in the liver, but it gave no clue to the primary cause of death. The biopsies in cases 1 and 51 (table 2) were done several months prior to death, at which time the primary cause was not suspected. There-

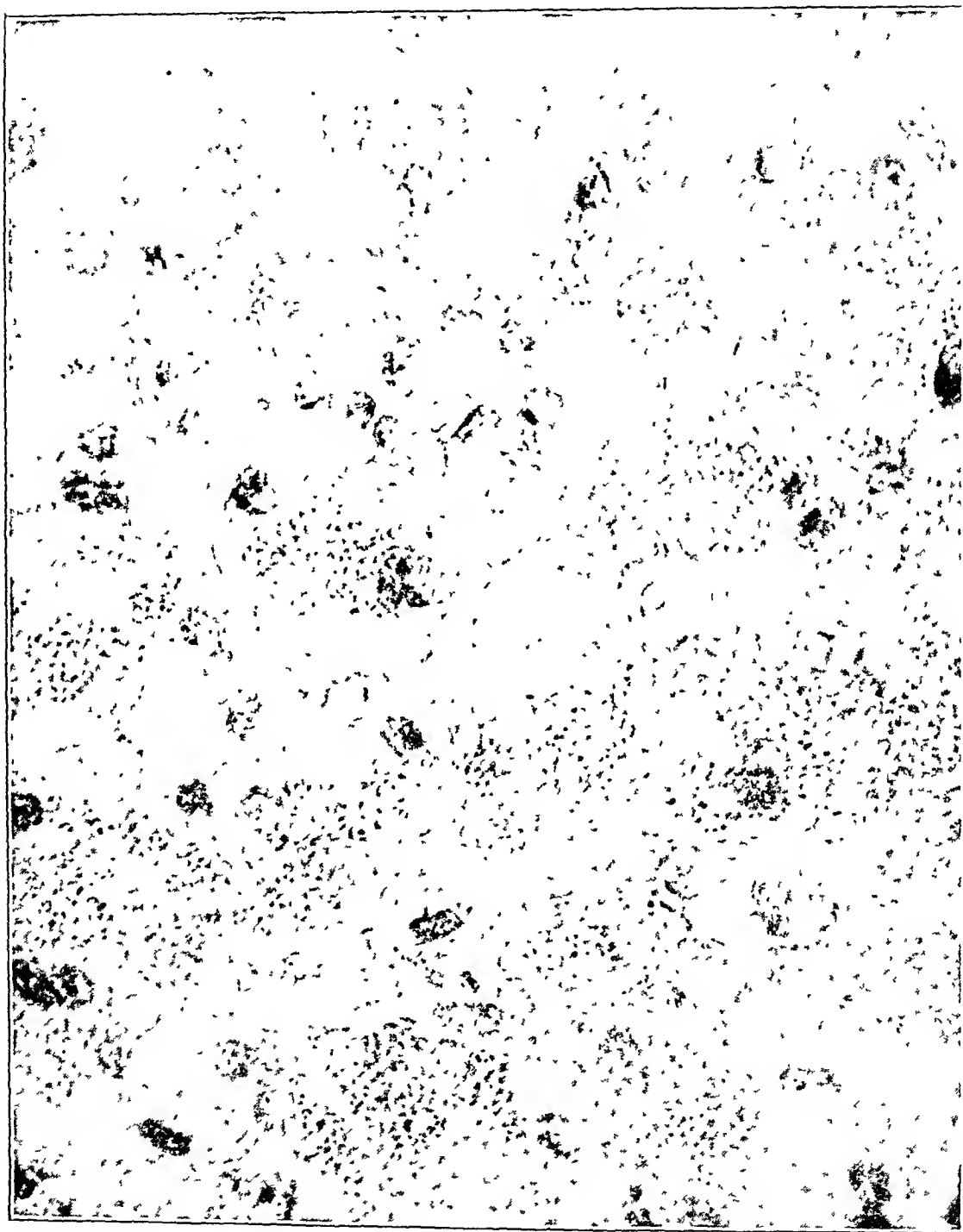


Fig. 10.—Brown degeneration of the liver of a patient with carcinoma of the colon.

fore, these two biopsies were considered to be diagnostic of the condition at that time. Analysis of these results reveals that in 14 cases (87.5 per cent) the diagnosis was either established or confirmed by biopsy of the liver.

## REPORT OF CASES

CASE 1.—A. D., a 51 year old white man, was admitted to the hospital Dec. 30, 1946, complaining of cough, pain in the chest, chills, fever and hemoptysis of three days' duration. The patient was known to be diabetic for the past five years and had had one previous admission for control of his diabetes, during which a cutaneous test for hemochromatosis (Fishback) was reported as giving negative results. Physical examination revealed typical signs of pneumonia involving the lower lobe of the left lung. The liver was enlarged 6 cm. below the right costal margin and was smooth and nontender. The skin revealed generalized brownish dusky discoloration. A diagnosis of pneumonia was made and confirmed. The patient responded to treatment, and a biopsy of the liver was performed on

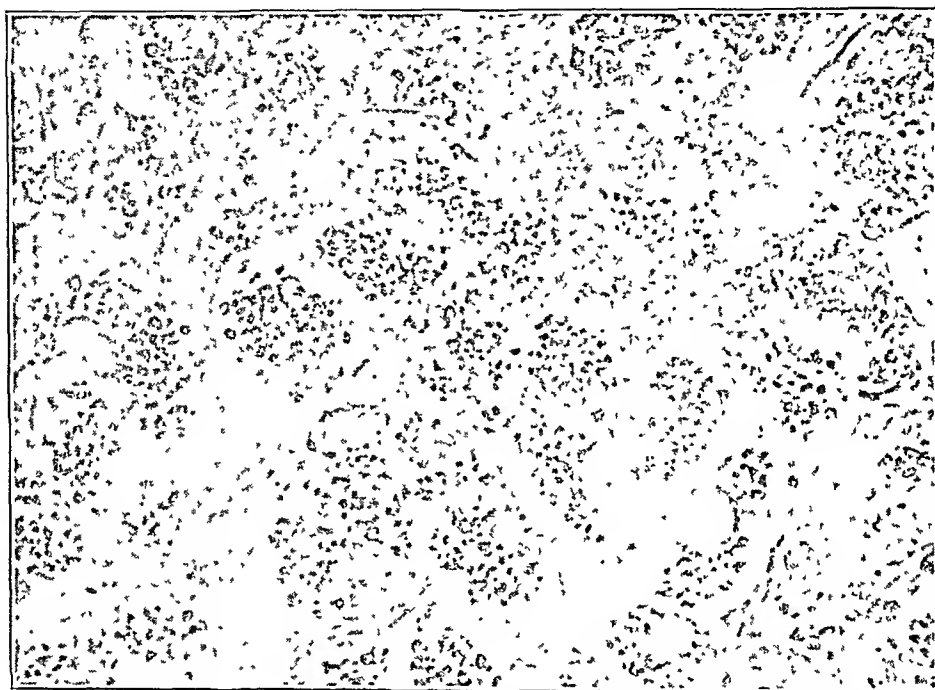


Fig. 11.—Hemosiderosis of the liver of a patient with hemochromatosis (iron stain).

December 12, because hemochromatosis was suspected. The report revealed the periportal connective tissue and the hepatic cells to be stippled with numerous pigment granules, which special stains showed to be iron, thus confirming the clinical diagnosis (fig. 11). A second Fishback test elicited negative results. The patient continued to improve and was discharged Jan. 27, 1947.

CASE 2.—W. S., a 53 year old white man, was admitted to the hospital March 21, 1946, complaining of fulness and tenderness in the tissues about the left eye. The present illness dated back to early in 1944, when the patient first noted swelling and pain in the left eye. He was admitted to the hospital in June 1944, at which time a diagnosis of melanosaarcoma of the left eyeball was made and the eye enucleated. Physical examination revealed a well developed white man, with dis-

coloration and tenderness about the left orbital cavity. The liver extended down to the right iliac crest and below the navel in the midline. Roentgenograms of the chest revealed no metastatic lesions. Two biopsies of the liver were performed, the first, on June 25, 1946, showing normal hepatic tissue. The second biopsy, performed August 2, revealed melanosarcoma comprising the entire specimen (fig. 12). The patient's course was progressively downhill, and he died Jan. 7, 1947. Permission for autopsy was not obtained.

These cases illustrate instances in which biopsy of the liver proved to be the diagnostic measure. The intradermal cutaneous test for hemochromatosis as suggested by Fishback has not been a reliable one in our experience, a positive result being observed in only 1 of our 4 cases. In addition, a biopsy of the skin did not reveal hemochromatosis

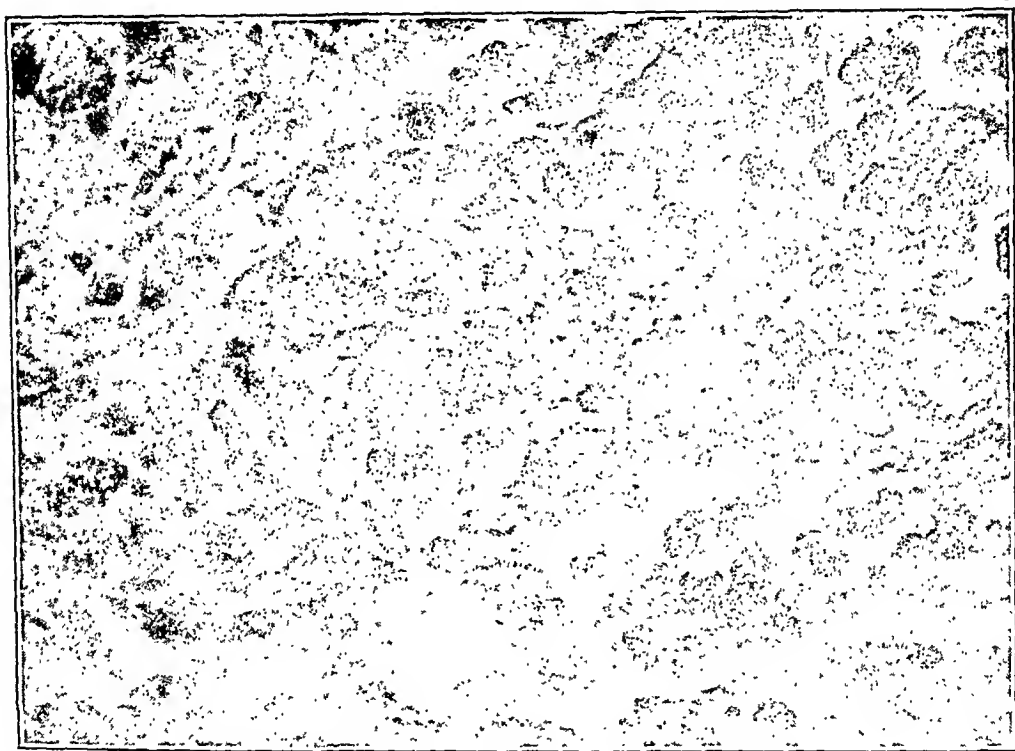


Fig. 12.—Melanosarcoma of the liver of a patient with retrobulbar melanosarcoma (special stain).

in 1 case. While the presence of metastatic lesions in the liver was suspected in the second case, this was not proved until after biopsy of the liver. Metastatic lesions elsewhere could not be demonstrated by the usual means.

CASE 3.—A. H., a 47 year old white man, was admitted to the hospital complaining of weakness and painless intermittent jaundice of nine months' duration. His stools had been acholic at times and his urine dark. He had lost 20 pounds (about 9 Kg.) in weight since the onset of his illness. Previous gastrointestinal roentgenograms revealed no abnormalities. Physical examination revealed the patient to be extremely jaundiced. The liver was palpable 10 cm. below the right costal margin and was nodular and tender. Gastrointestinal roentgenograms while the patient was in the hospital again failed to reveal abnormalities. Examination



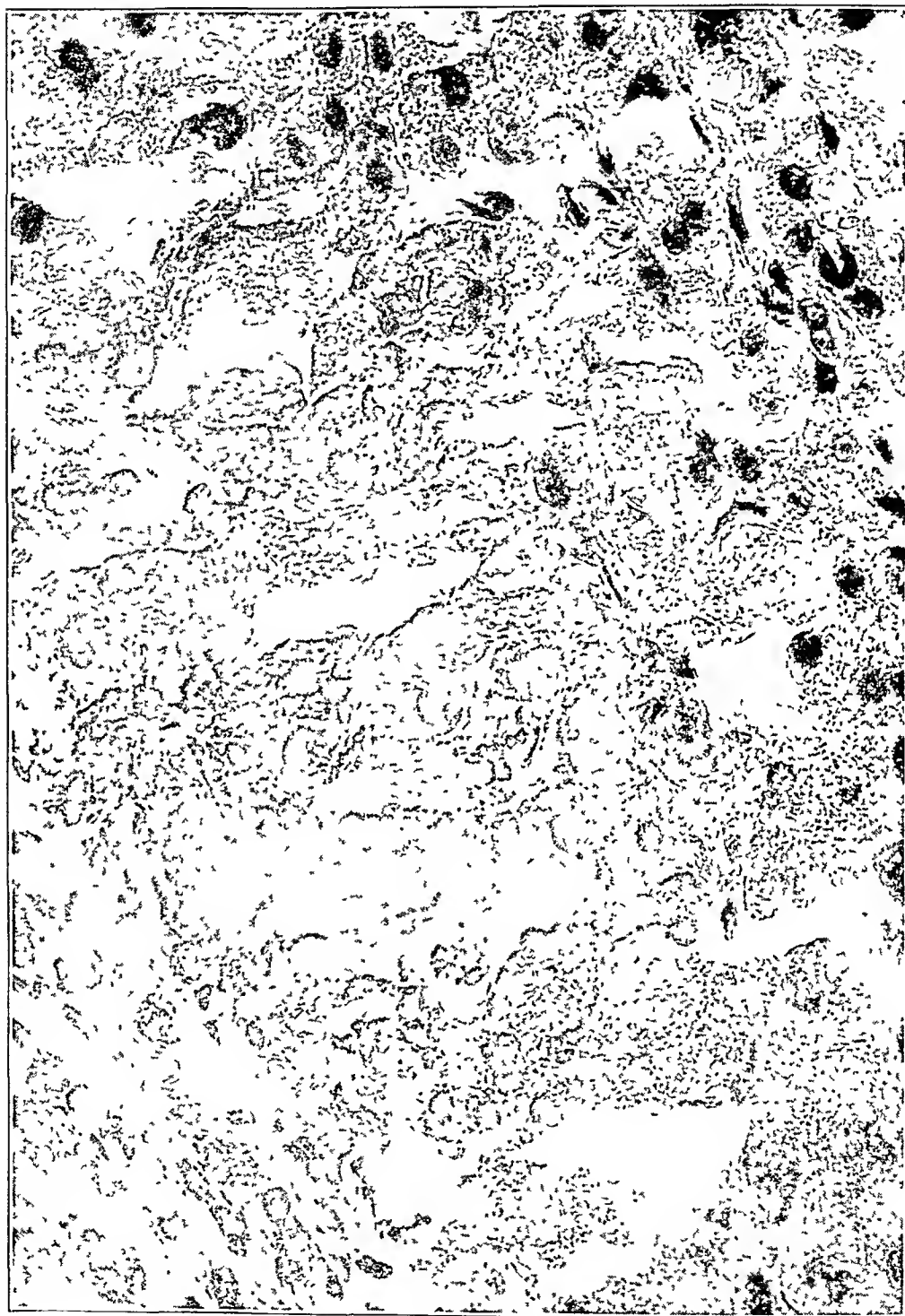


Fig. 13—Decided biliary cirrhosis of the liver.

of the blood revealed moderate anemia, and results of urinalysis were positive for bile and negative for urobilinogen on many occasions. The icterus index varied from 65.0 to 152.0, with a direct immediate van den Bergh reaction. Biopsy of the liver was performed on Sept. 28, 1946, and revealed biliary type hepatic cirrhosis (fig. 13). After several transfusions, a laparotomy was performed on October 25, which revealed obstruction of the distal common duct, with biliary cirrhosis. The cause of this obstruction could not be determined, and a cholecystogastrostomy was performed. A biopsy of the pancreas was made, and the patient later had abdominal hemorrhage and fibrinous peritonitis and died November 2. Autopsy revealed the cause of the obstruction to be an extremely small carcinoma of the ampulla of Vater.

CASE 4.—W. G., a 52 year old white man, was admitted to the hospital Feb. 26, 1946, because of ankylosis of the jaw. The patient gave a history of joint

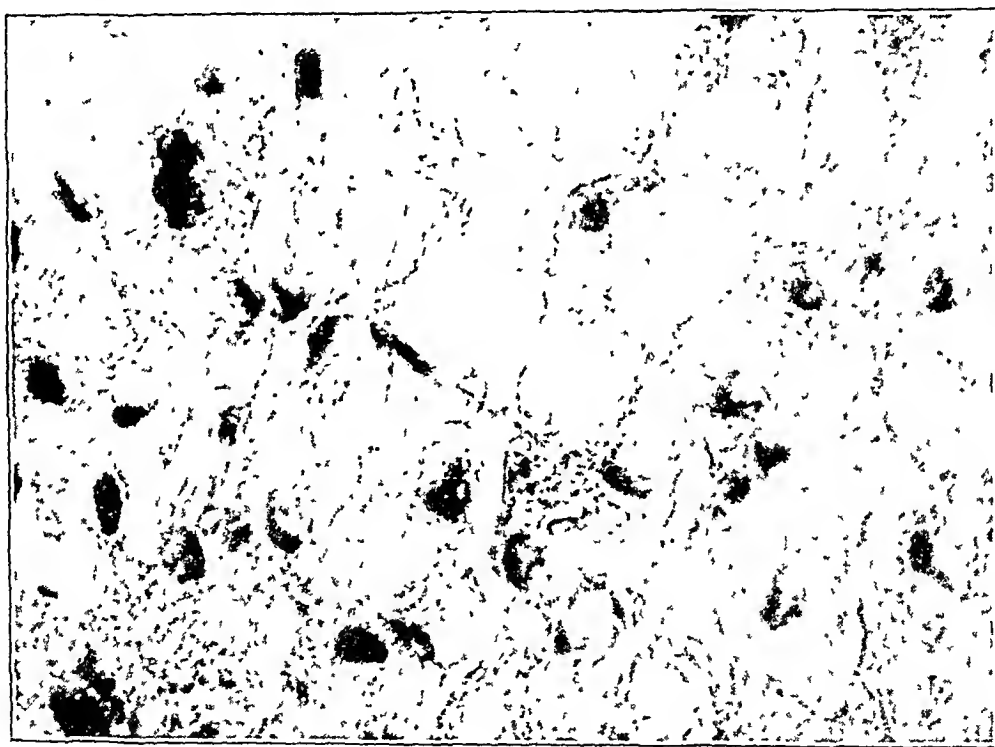


Fig. 14.—Amyloidosis of the liver, with almost complete destruction of architecture (special stain).

pain and later ankylosis, dating back twenty-nine years. Physical examination revealed an emaciated man with the typical signs of rheumatoid arthritis involving the shoulders, hands and knees bilaterally. In addition, there was a so-called "poker spine" and ankylosis of both temporomandibular joints. The liver was palpable at the right iliac crest and was smooth and nontender. Because amyloidosis of the liver was suspected, a biopsy was performed October 19. The liver revealed advanced amyloid degeneration (fig. 14). The congo red test resulted in the retention of less than 20 per cent of the dye in the blood in one hour.

In case 3, the biopsy of the liver differentiated jaundice due to obstruction and that due to parenchymatous hepatic disease or cholangiolitis, thereby justifying laparotomy. This particular biopsy cannot be called a diagnostic one in the strict sense of the term, since

the underlying cause of the jaundice remained obscure until autopsy, but it was in agreement with the clinical picture. In case 4, the suspicion of amyloidosis of the liver was confirmed.

CASE 5.—A. B., a 54 year old white man, was admitted to the hospital complaining of sharp pains around the umbilicus, anorexia, watery diarrhea and a loss of 15 pounds (about 7 Kg.) in weight, of five weeks' duration. Physical examination showed an emaciated patient who appeared chronically ill. The abdomen was distended and the liver greatly enlarged and nodular, extending down to the right iliac crest and to the level of the navel in the midline. Examination of the blood revealed moderate anemia, which became progressively severer. Roentgenograms of the gastrointestinal tract, kidneys, ureter and bladder revealed evidence of a mass in the abdomen, but none of them localized the lesion to any one organ. Biopsy of the liver was performed on June 26, 1946, and

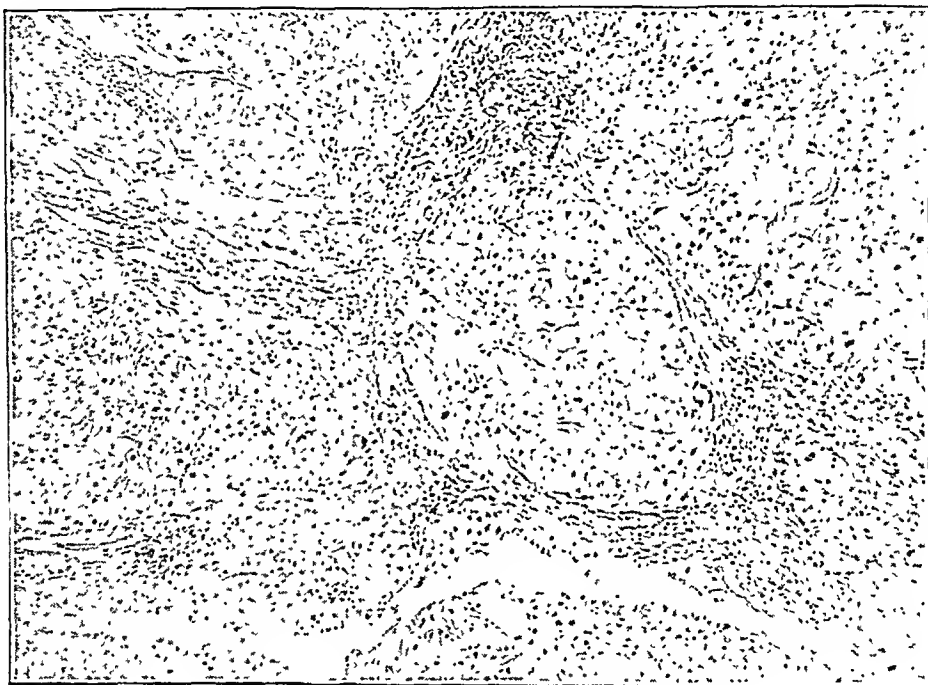


Fig. 15.—Advanced portal cirrhosis of the liver (Van Gieson stain).

showed normal hepatic tissue. The patient became progressively weaker and died July 24. Autopsy revealed a carcinoma of the splenic flexure of the colon, with metastasis to all the abdominal organs, especially the liver. It was noted that the biopsy needle had been inserted into the liver and had passed within several millimeters of two metastatic tumor nodules.

CASE 6.—M. P., a 45 year old Mexican woman, was admitted to the hospital April 19, 1946, with the complaint of weakness, anorexia, vomiting and abdominal pain and distention of one month's duration. The patient had noted jaundice for four days prior to admission. There was a history of chronic alcoholism of long duration. Physical examination revealed an emaciated patient in some distress. The liver was enlarged 10 cm. below the right costal margin and was smooth and moderately tender. There was slight icterus of the scleras and mucous membranes. Numerous procedures, including roentgenograms of the chest and gastro-

intestinal tract and examination of abdominal fluid and sputum failed to reveal any specific diagnosis. A biopsy of the liver, performed on September 14, revealed advanced portal cirrhosis (fig. 15). The patient pursued a downhill course and died September 23. Autopsy revealed chronic miliary tuberculosis, involving the lungs, intestines and peritoneum, with portal cirrhosis and bronchopneumonia.

The aforementioned cases illustrate instances in which the biopsy of the liver was not in agreement with the clinical picture. Case 5 is an example of one of the limitations inherent in the procedure. In case 6, the report of biopsy might be considered misleading, since the clinical picture was not clearcut and the presence of portal cirrhosis, diagnosed at biopsy, provided definite evidence of a condition which could satisfactorily explain it. Thus, the diagnosis of tuberculosis was given less prominence than it would have been had normal hepatic tissue been obtained.

#### COMMENT

From a clinical standpoint, biopsies may be classified into those which are helpful in determining the diagnosis and those which are not. Included in the helpful group are those biopsies which are diagnostic and those which are in agreement with the clinical picture, but which do not reveal the underlying pathologic condition. Biopsies considered not to be helpful are those which were not in agreement with the clinical picture and the failures. The classification is, of course, subjective to a certain extent. On this basis, eighty-three biopsies (75 per cent) were considered helpful and twenty-eight biopsies (25 per cent) not helpful. If the 14 cases in which no tissue was obtained for study are eliminated, 86 per cent of the biopsies were observed to aid in the diagnosis. These observations compare favorably with those of other writers.<sup>28</sup>

The specimen of liver obtained in our cases consisted of a core of tissue from 10 to 20 mm. in length and approximately 2 mm in width. From the pathologic standpoint, these specimens offer the advantages of minimum autolysis, which permits a cytologic study generally superior to that afforded at autopsy. The specimens fixed in alcohol for the purpose of studies of glycogen are admittedly more satisfactory than specimens obtained at autopsy. In addition, biopsy may be performed at intervals, thus enabling one to follow the progress of pathologic changes and to evaluate the effects of treatment.

The principal disadvantage of the specimen is its size, which offers a relatively small area for visualization. Thus, a completely objective diagnosis is sometimes not possible. Compression and shredding of the specimen during the biopsy procedure causes distortion of the tissues in some instances. Comparison of the specimens obtained at autopsy and

28. Hoffbauer, Evans and Watson.<sup>23</sup> Davis, Scott and Lund.<sup>24</sup>

those obtained by biopsy revealed that in a majority of cases the biopsy specimen was a good sample of the changes in the entire liver. This has been commented on by Sherlock.<sup>14</sup>

Although not within the scope of this paper, it is interesting to note the correlation of tests of hepatic function with the pathologic changes revealed by biopsy. Two or more tests of hepatic function were performed on 74 patients in this series. After reviewing these determinations and comparing them with the pathologic observations in the biopsy specimen, we were unable to correlate the results. Cases in which the disease was classified as early portal cirrhosis by means of the biopsy sometimes revealed significant impairment in one or several tests of hepatic function, while in many instances the cases of far advanced disease revealed little impairment. This is in agreement with the report of Hoffbauer, Evans and Watson.<sup>23</sup> The lack of correlation was evident also in some of the cases of metastatic carcinoma of the liver. In a review of macrocytosis associated with disease of the liver, Weintrobe<sup>29</sup> stated that this observation was present in 32.6 per cent of 132 cases of varied forms of hepatic disease, and he pointed out that this is noted only in cases of hepatic disease of long duration and of wide extent. Hematocrit studies were done in 29 of our cases, and macrocytosis (mean cell volume more than 95.0 cubic microns) was observed in 18 cases (62 per cent). There was no anemia in 17.2 per cent, macrocytic anemia in 55.3 per cent, normocytic anemia in 17.2 per cent and microcytic anemia in 10.3 per cent. Chronic loss of blood was a factor in most of the last-mentioned group.

We believe that needle biopsy of the liver has established itself as a valuable aid in the diagnosis of diseases of the liver. As previously stated, the clinical picture is often confusing, and in the majority of our cases the biopsy confirmed clinical impressions or revealed the presence of an unsuspected lesion. In addition to the use of biopsy of the liver in any case of hepatomegaly of undetermined origin, the fact that several biopsies may be performed on patients over a period of time permits an evaluation of treatment in chronic hepatic diseases, such as cirrhosis. The procedure also affords an opportunity for vital studies of living hepatic tissue, which may aid materially in elucidating the normal physiologic function of the liver or alteration of its metabolic processes and, as has been reported frequently since 1939, an investigation of hepatic changes in epidemic hepatitis, toxic hepatitis and spirochetal jaundice (Weil's disease).

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29. Weintrobe, M. W.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1946, p. 399.

Limitations of the procedure are those associated with random sampling which may miss a focal lesion, as illustrated in 1 case (case 5). Biopsies performed in 2 cases of polycystic disease of the liver, as proved by laparotomy, failed to yield any tissue. Thus, hepatic disease of a diffuse nature is most readily detectable.

The hazards associated with the intercostal approach in biopsy of the liver are apparent on reviewing the papers in which this method was used. The greatest danger is hemorrhage, as pointed out by Raby,<sup>30</sup> in 1944, in a review of 7 previously reported cases of fatal hemorrhage, to which he added 1 case of his own. This was also commented on by Toullec and Huard.<sup>31</sup> The bleeding in these cases was attributed to the fact that the needle is held firmly between the ribs and the liver is torn as it moves coincident with respiration. In addition, the pleural sac is exposed to the danger of infection in this approach. The procedure requires the complete cooperation of the patient, who must hold his breath in expiration during the entire time the needle is inserted, the syringe attached and the needle advanced into the liver and withdrawn. Because of these potential dangers, we join other writers<sup>32</sup> in recommending that biopsy of the liver be performed from a subcostal approach only and that the liver be palpated at least 4 cm. below the thoracic cage.

Other complications include the introduction of infection into the peritoneal cavity or the abdominal wall and perforation of, or injury to, nearby viscera, such as the intestines, gallbladder, kidneys, adrenals or pancreas. Baron<sup>17</sup> reported the recovery of a piece of colonic mucosa in 1 case, without untoward results. Davis, Scott and Lund<sup>24</sup> reported puncture of the gallbladder by transfixing the right lobe of the liver in 1 case and obtained duodenal mucosa in another, without complications. Further precautions include determination of the bleeding, clotting and prothrombin times, especially in jaundiced patients. The prothrombin time (Quick's method) was performed in 47 of our cases. Vitamin K preparations were administered when indicated, and tests of the prothrombin time were repeated prior to biopsy in these instances. Biopsies of the liver should be avoided in the region of the gallbladder and are precluded in the presence of severe ascites and abdominal distention secondary to ileus.

If the aforementioned precautions are observed, needle biopsy of the liver carries with it relatively little risk and yields valuable information in the majority of cases.

30. Raby, K.: Complications and Dangers of Liver Biopsy, *Nord. med. (Hospitalstid.)* **24**:2161-2164 (Dec. 8) 1944.

31. Toullec, F., and Huard, P.: La ponction exploratrice du foie (dangers, indications, contre-indications), *Monde méd., Paris* **45**:990-999 (Nov. 15) 1935.

32. Baron.<sup>17</sup> Tripoli and Fader.<sup>21</sup> Hoffbauer.<sup>22</sup> Davis, Scott and Lund.<sup>24</sup>

## SUMMARY

One hundred and eleven biopsies of the liver in 100 patients, with the Vim-Silverman needle, are reported. Of these, ninety-seven biopsies (87.4 per cent) were successful and fourteen biopsies (12.6 per cent) were failures. There were no fatalities or serious complications. Of the successful biopsies, eighty-three (86 per cent) were considered to be helpful in the diagnosis.

The indications and complications of needle biopsy of the liver have been pointed out and commented on.

We recommend that biopsy be performed only when the liver is easily palpable. The intercostal approach is not advocated, and biopsies should be avoided in the region of the gallbladder and in cases of ascites and abdominal distention due to ileus. In addition, bleeding, clotting and prothrombin times should be normal, and facilities for blood transfusion should be readily available.

NOTE.—Since this paper was submitted for publication we have performed two hundred and fifty additional biopsies of the liver, using the same technic and criterion. There have been no fatalities in our series to date, and only 4 patients showed clinical evidence of hemorrhage, all of whom responded to conservative therapy.

870 West Wisconsin Avenue.

# PLASMA LIPIDS IN PRIMARY (XANTHOMATOSIS) AND SECONDARY HYPERCHOLESTEREMIA

## I. The Effect of Lipotropic Substances

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**H**YPERCHOLESTEREMIA is a common observation in some well recognized metabolic disorders. The elevated level of cholesterol in the serum may represent a primary defect in the metabolism of this sterol (xanthomatosis)<sup>1</sup> or may signify a derangement in lipid metabolism secondary to some underlying metabolic disturbance, such as diabetes mellitus, hypothyroidism and nephrosis. The present study embraces both types of hypercholesteremia. The first part of the investigation is concerned with the effect of several lipotropic substances on the plasma lipids and the second, which will be reported later, with diets low in cholesterol values.

## MATERIAL AND METHODS

Thirteen patients were studied. The disease in 9 of these was classified as primary (essential) xanthomatosis with hypercholesteremia<sup>2</sup> and in 4 as secondary hypercholesteremia due to various metabolic disorders. The clinical data on these patients are detailed in table I.

The following lipotropic materials<sup>3</sup> were used (oral route): (a) vitamin E, synthetic d,l-alpha-tocopherol acetate or mixed natural tocopherols, in 7 patients with primary (essential) xanthomatosis, for twelve to fifty weeks (table 2), (b)

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Aided by a grant from the New York Diabetes Association.

From the Division of Cardiology and the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, New York.

1. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, *Ann. Int. Med.* 11:1662-1746 (March) 1938. Thannhauser, S. J.: *Lipidoses: Diseases of the Cellular Lipid Metabolism*, New York, Oxford University Press, 1940.

2. Dr. H. H. Ritter referred to us the patients in cases 2 and 3.

3. Hoffman-LaRoche, Inc., Nutley, N. J., supplied the d,l-alpha-tocopherol; Eli Lilly and Company, Indianapolis, supplied the mixed natural tocopherols; the American Lecithin Co., Inc., Elmhurst, N. Y., supplied the oil-free and crude lecithin; Dr. Lester R. Dragstedt, Chicago, supplied the lipocaic, and Sharpe & Dohme, Inc., Philadelphia, supplied the pancreatic extract.



oil-free or crude lecithin in, 4 patients with primary (essential) xanthomatosis, for eight to fifteen weeks (table 3), (c) lipocai<sup>4</sup> or pancreatic extract with lipocai-like properties, in 1 patient with primary (essential) xanthomatosis, for twenty-four and fourteen weeks, respectively (table 4), and (d) vitamin E, d,l-alpha-tocopherol acetate or mixed natural tocopherols, in 4 patients with secondary

TABLE 1.—*Clinical Data for 9 Patients with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type and 4 Patients with Secondary Hypercholesteremia Herein Investigated*

Case No.	Age (Yr.)	Sex	Relationship	Diagnosis	Comment
1	35	M	-----	Xanthoma tuberosum; xanthomatous tendon sheath tumor; probable xanthomas of coronary arteries	Acute posterior myocardial infarct at age of 33
2	35	M	Brother of patient in case 3	Xanthomatous tendon sheath tumor	-----
3	34	F	Sister of patient in case 2	Xanthomatous tendon sheath tumor	
4	18	F	-----	Arcus juvenilis (xanthomatous involvement of cornea); xanthoma tuberosum; probable xanthomatous involvement of endocardium; probable xanthomas of coronary arteries	Harsh high pitched precordial murmur; T waves in leads II and III of the electrocardiogram were sharply and deeply inverted; cardiac failure developed in December 1944 and 3 weeks later the patient died suddenly while defecating
5	11	M	Brother of patient in case 6	Arcus juvenilis (xanthomatous involvement of cornea); xanthoma tuberosum; probable xanthomatous involvement of endocardium	Harsh high pitched systolic murmur, loudest at aortic area; harsh, low pitched, systolic murmur, loudest at mitral area
6	14	M	Brother of patient in case 5	Xanthomatous involvement of tendon sheaths	-----
7	49	F	-----	Xanthoma tuberosum	-----
8	44	F	-----	Xanthoma tuberosum	-----
9	35	M	-----	Xanthoma tuberosum	-----
12	49	M	-----	Diabetes mellitus	Mild degree; good control with little or no insulin; glycosuria and hyperglycemia rare
13	72	F	-----	Cholecystitis and cholelithiasis	-----
14	39	M	-----	Diabetes mellitus; chronic nephritis	Possibility of intercapillary glomerulosclerosis
15	45	M	-----	Diabetes mellitus	Possibility of primary (essential) xanthomatosis, because of associated splenomegaly and leukopenia, but this diagnosis not definitely established

hypercholesteremia due to various metabolic disturbances (e.g., diabetes mellitus, cholecystitis and cholelithiasis, and chronic nephritis), for six to twelve weeks (table 5).

Prior to the administration of the lipotropic substances, two or three fasting serum cholesterol determinations were made at intervals of one or two weeks

4. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, *Am. J. Physiol.* 117:175-181 (Sept.) 1936.

except in case 3 (table 2) and cases 12, 13, 14 and 15 (table 5), in which only one control observation was made. In several studies (tables 2 and 5) the total lipids and fatty acids in the plasma were also estimated.<sup>5</sup> In most instances, the plasma lipids or serum cholesterol determinations were made at intervals of two weeks during the experimental period:

The total plasma lipids were estimated by the procedure of Bloor.<sup>6</sup> Plasma or serum cholesterol was determined by the method of Sackett.<sup>7</sup> Total fatty acids were calculated by the difference between total lipids and cholesterol values.<sup>6b</sup> The range for these lipid components in normal subjects by these procedures is as follows: cholesterol 160 to 230 mg. per hundred cubic centimeters, total lipids 500 to 700 mg. per hundred cubic centimeters and total fatty acids 200 to 420 mg. per hundred cubic centimeters.

### RESULTS

Table 2 shows that the ingestion of d,l-alpha-tocopherol acetate or mixed natural tocopherols over a period of twelve to fifty weeks by 7 patients with primary (essential) xanthomatosis and hypercholesteremia failed to decrease the level of the blood lipids. The decrease in the serum cholesterol in the patient (case 3) with xanthomatous tendon sheath tumor may be ascribed to the diet low in cholesterol which was simultaneously prescribed, since discontinuation of the diet on the thirty-first week of observation was promptly followed by an increase in the serum cholesterol even though the administration of tocopherols was uninterrupted.

Table 3 reveals that the ingestion of oil-free or crude lecithin, in appreciable doses over a period of eight to fifteen weeks by 4 patients with primary (essential) xanthomatosis, likewise failed to decrease the level of the serum cholesterol.

In 1 patient with arcus juvenilis, xanthoma tuberosum and probable xanthomatous involvement of the endocardium (case 5), the oral administration of 6 Gm. of lipocaic per day for twenty-four weeks followed by administration of 6 Gm. of pancreatic extract with lipocaic-like properties for an additional fourteen weeks did not diminish the serum cholesterol (table 4).

Table 5 shows that the oral administration of d,l-alpha-tocopherol acetate or mixed natural tocopherols, over a period of six to twelve

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5. Miss Frances Lauber gave technical assistance.

6. (a) Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: The Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J. Biol. Chem.* **52**:191-205 (May) 1922. (b) Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, *J. ibid.* **77**:53-73 (April) 1928.

7. Sackett, G. E.: Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, *J. Biol. Chem.* **64**:203-205 (May) 1925.

TABLE 2.—Effect of Vitamin E on the Plasma Lipids of 7 Patients with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type

Case No.	Blood Lipids (Mg./100 Cc.) and Medication	Weeks of Study								Comment
		0	2	4	6	8	10	12	14	
1	Total lipids	1,780	1,874	1,972	1,685	1,645	1,530	1,822	--	Serum cholesterol determinations continued for 47 weeks (8 additional analyses); values ranged from 330 to 530 mg., with an average of 450 mg. per 100 cc.; medication consisted of 300 mg. of mixed natural tocopherols per day except for the twentieth to twenty-fourth week, when no medication was given
	Fatty acids	1,370	1,424	1,554	1,299	1,232	1,232	1,344	--	
	Cholesterol	410	450	418	386	413	417	478	390	
	Tocopherols per day (mg.)	None	None	None	300*	300*	300†	300†	300†	
2	Cholesterol	375	335	445	--	300†	--	290	305	Serum cholesterol determinations continued for 22 weeks (2 additional analyses); values were 445 and 375 mg., with an average of 410 mg. per 100 cc.; medication consisted of 300 mg. of mixed natural tocopherol per day
	Tocopherols per day (mg.)	None	None	None	300†	300†	300†	300†	300†	
	Total lipids	1,116	800	1,093	--	--	--	--	--	
	Fatty acids	676	397	665	--	--	--	--	--	
3	Cholesterol	440	403	428	300†	355	300†	295	--	Serum cholesterol determinations continued for 50 weeks (4 additional analyses); low cholesterol diet and mixed tocopherols were continued until the twenty-fourth week, when the serum cholesterol was 300 mg. per 100 cc.; thereafter a low cholesterol diet alone was prescribed and the serum cholesterol at the thirty-first week was 195 mg. per 100 cc.; patient voluntarily discontinued the diet from the thirty-first week on; serum cholesterol at the thirty-fifth and fiftieth week of observation was 315 and 355mg. per 100 cc., respectively
	Tocopherols per day (mg.)	None	300†	300†	300†	300†	300†	300†	--	
	Total lipids	1,709	1,808	1,770	--	1,811	--	1,587	1,674	
	Fatty acids	1,006	1,183	1,157	--	1,186	--	993	1,014	
5	Cholesterol	703	625	613	--	625	--	594	630	-----
	Tocopherols per day (mg.)	None	None	None	75*	75*	75*	75*	300†	
	Total lipids	1,358	1,525	1,774	--	1,381	1,455	1,352	--	
	Fatty acids	810	895	1,174	--	834	912	761	--	
6	Cholesterol	548	630	600	--	547	543	588	--	Serum cholesterol determinations continued for 40 weeks (5 additional analyses); values ranged from 420 to 895 mg. per 100 cc.; with an average of 686 mg.; medication consisted of 300 mg. of mixed natural tocopherols per day except for the eighteenth to twenty-second week, when no medication was given
	Tocopherols per day (mg.)	None	None	None	75*	75*	300†	300†	--	
	Total lipids	2,297	2,176	2,877	2,943	2,448	2,552	1,860	--	
	Fatty acids	1,737	1,576	2,230	2,273	1,788	1,899	1,225	--	
7	Cholesterol	560	600	647	670	660	653	635	--	Serum cholesterol determinations continued for 22 weeks (2 additional analyses); values were 660 and 740 mg., with an average of 700 mg. per 100 cc.; no medication given
	Tocopherols per day (mg.)	None	None	None	300*	300*	300†	300†	--	
	Total lipids	1,860	1,756	1,795	1,729	1,823	1,600	--	--	
	Fatty acids	1,245	1,256	1,270	1,229	1,323	1,150	--	--	
8	Cholesterol	615	500	525	500	500	450	475	543	
	Tocopherols per day (mg.)	None	None	None	150*	300*	300*	300†	300†	
	Total lipids	1,860	1,756	1,795	1,729	1,823	1,600	--	--	
	Fatty acids	1,245	1,256	1,270	1,229	1,323	1,150	--	--	

\*In the form of d,l- $\alpha$ -tocopherol acetate.

†Mixed natural tocopherols.

‡With a diet low in cholesterol content.

weeks, to 4 patients with secondary hypercholesteremia due to recognizable metabolic defects (diabetes mellitus, cholecystitis and cholelithias, chronic nephritis) failed to decrease the level of the plasma

TABLE 3.—*Effect of Lecithin on the Serum Cholesterol of Patients with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type*

Case No.	Serum Cholesterol (Mg./100 Cc.) and Medication	Weeks of Study													
		0	2	3	4	5	6	7	8	9	10	12	1	15	
1	Serum cholesterol	410 450 418	--	335	--	290	--	440	--	335	--	--	--	--	
	Lecithin per day (Gm.)	None	24*	24*	24*	24*	24*	24*	24*	24*	--	--	--	--	
2	Serum cholesterol	375 355 445	--	--	355	--	375	--	395	--	--	--	--	--	
	Lecithin per day (Gm.)	None	24*	24*	24*	12*	12*	12*	12*	--	--	--	--	--	
4	Serum cholesterol	525 530	--	--	535	--	485	--	610	--	565	--	490	475	
	Lecithin per day (Gm.)	None	18†	18†	18†	18†	18†	27‡	27‡	27‡	27‡	54°	54°	54°	
9	Serum cholesterol	375 420 350	420	--	460	--	355	--	360	--	510	340	--	--	
	Lecithin per day (Gm.)	None	24*	24*	24*	36‡	36‡	36‡	36‡	36‡	36‡	18†	--	--	

\*Oil-free lecithin (granulated phosphatides).

†Six "lexo wafers." (Each wafer contains 3 Gm. of soybean lecithin, 1,000 U. S. P. units of vitamin A, 100 U. S. P. units of vitamin D, 165 U. S. P. units of thiamine and 81 mg. of phosphorus.)

‡Nine "lexo wafers."

°Eighteen "lexo wafers."

\*Eight "lexo wafers."

†Twelve "lexo wafers."

TABLE 4.—*The Effect of Pancreatic Extracts on the Serum Cholesterol of a Patient with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type (Case 5)*

Weeks	Lipocaic per Day (Gm.)	Pancreatic Extract per Day (Gm.)	Serum Cholesterol (Mg./100 Cc.)
0	-----	-----	703 625 613
5	6	-----	700
8	6	-----	580
15	6*	-----	490
21	6†	-----	660
24	6	-----	680
28	-----	6	535
32	-----	6	500
35	-----	6	510
38	-----	6	810

\*The patient received no lipocaic for fourteen days during this period, because of disease of the respiratory tract.

†The patient took no lipocaic for eight days before determination of serum cholesterol.

cholesterol. In 2 patients (cases 12 and 13) there was a suggestive fall in the total plasma lipids and fatty acids, but the plasma cholesterol remained unchanged.

COMMENT

The lipotropic effect of vitamin E was first described by Dam and Kelman,<sup>8</sup> who demonstrated a reduction in the fasting plasma lipids of vitamin E-deficient chicks after the administration of vitamin E. Subsequent studies by Dam<sup>9</sup> and by Bruger<sup>10</sup> showed that the atherosclerosis produced in rabbits fed a diet high in cholesterol was not diminished by

TABLE 5.—Effect of Vitamin E on the Plasma Lipids of Patients with Hypercholesteremia Due to Metabolic Disturbance Other Than Xanthomatosis

Case No.	Blood Lipids (Mg./100 Cc.) and Medication	0	Weeks of Study					
			2	4	6	8	10	12
12	Total lipids	1,770	--	1,478	1,536	1,490	1,265	1,029
	Fatty acids	1,192	--	970	1,020	995	797	506
	Cholesterol	578	--	508	516	495	468	523
	Tocopherols per day (Mg.)	None	150*	150*	300*	300*	300 <sup>o</sup>	300 <sup>o</sup>
13	Total lipids	1,044	--	--	920	--	--	--
	Fatty acids	714	--	--	592	--	--	--
	Cholesterol	330	--	--	328	--	--	--
	Tocopherols per day (Mg.)	None	150*	150*	150*	--	--	--
14	Total lipids	828	--	918	--	1,047	--	--
	Fatty acids	502	--	630	--	704	--	--
	Cholesterol	326	--	288	--	343	--	--
	Tocopherols per day (Mg.)	None	150*	150*	150*	150*	--	--
15	Total lipids	4,412	--	4,368	--	4,542	--	4,791
	Fatty acids	4,027	--	3,980	--	4,187	--	4,411
	Cholesterol	385	--	388	--	355	--	380
	Tocopherols per day (Mg.)	None	150*	150*	150*	150*	300 <sup>o</sup>	300 <sup>o</sup>

\*Synthetic d, l-alpha-tocopherol acetate.  
<sup>o</sup>Mixed natural tocopherols.

simultaneous administration of d,l-alpha-tocopherol acetate. On the contrary, Bruger, using dosages of vitamin E almost four times the dosage used by Dam demonstrated an appreciable increase in the amount of cholesterol deposited in the aorta. In the present study, no reduction in serum lipids was obtained following the prolonged administration of moderate or large doses of d,l-alpha-tocopherol acetate or mixed natural tocopherols to patients with primary (essential) xanthomatosis and hypercholesteremia. In 4 patients with secondary hypercholesteremia, vitamin E likewise failed to influence the level of the plasma cholesterol, but it apparently caused a reduction in the total plasma lipids and fatty acid in 2 of these patients.

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9. Dam, H.: Ineffectiveness of Vitamin E in Preventing Cholesterol Deposition in the Aorta, *J. Nutrition* **28**:289-295 (Oct.) 1944.  
10. Bruger, M.: Experimental Atherosclerosis: VII. Effect of Vitamin E, *Proc. Soc. Exper. Biol. & Med.* **59**:56-57 (May) 1945.

Soybean lecithin contains choline, inositol and cephalin in approximately equal proportions. In the wafer form, it contains soybean oil as a carrier. The granulated form, also used in this study, is oil-extracted lecithin. Both choline and inositol have been shown to have lipotropic properties. Many reports have appeared in the literature describing the effect of lecithin, choline or inositol in reducing hepatic lipid accumulation in rats which had been fed large amounts of saturated fats, cholesterol or vitamin B compounds.<sup>11</sup> Both Downs<sup>12</sup> and Kesten and Silbowitz<sup>13</sup> reported the prevention of cholesterol-induced atherosclerosis in rabbits by the simultaneous administration of lecithin. Andrews and Broun<sup>14</sup> obtained similar results with choline. Several reports have appeared describing the lipotropic activity of lecithin in human beings. Gröss and Kesten<sup>15</sup> observed a considerable fall in serum cholesterol in a patient with xanthelasma and decided hypercholesteremia following the daily administration of 60 Gm. of soybean lecithin for five weeks. There was a moderate drop with 4 Gm. given daily for sixteen weeks.

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11. Hershey, J. M.: Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, *Am. J. Physiol.* **93**:657-658 (June) 1930. Hershey, J. M., and Soskin, S.: Substitution of "Lecithin" for Raw Pancreas in the Diet of the Depancreatized Dog, *ibid.* **93**:74-85 (Aug.) 1931. Best, C. H.; Hershey, J. M., and Huntsman, M. E.: The Effect of Lecithine on Fat Deposition in the Liver of the Normal Rat, *J. Physiol.* **75**:56-66 (May) 1932. Best, C. H., and Huntsman, M. E.: The Effects of the Components of Lecithin upon Deposition of Fat in the Liver, *ibid.* **75**:405-412 (Aug.) 1932. Best, C. H., and Ridout, J. H.: The Effects of Cholesterol and Choline on Deposition of Liver Fat, *ibid.* **78**:415-418 (July) 1933. Best, C. H.; Channon, H. J., and Ridout, J. H.: Choline and the Dietary Production of Fatty Livers, *ibid.* **81**:409-421 (July) 1934. Maclean, D. L.; Ridout, J. H., and Best, C. H.: Effects of Diets Low in Choline upon Liver Function, Growth, and Distribution of Fat in the White Rat, *Brit. J. Exper. Path.* **18**:345-354 (Oct.) 1937. Gavin, G., and McHenry, E. W.: Inositol: A Lipotropic Factor, *Letters to the Editors, J. Biol. Chem.* **139**:485 (May) 1941. McHenry, E. W., and Gavin, G.: Effects of Inositol upon Liver Fat in the Rat, *Federation Proc.* **1**:124-125 (March) 1942. Engel, R. W.: The Relation of B-Vitamins and Dietary Fat to the Lipotropic Action of Choline, *J. Nutrition* **24**:175-185 (Aug.) 1942. McHenry, E. W., and Patterson, J. M.: Lipotropic Factors, *Physiol. Rev.* **24**:128-167 (Jan.) 1944.

12. Downs, W. G., Jr.: Lecithin in Experimental Arteriosclerosis: A Preliminary Study, *Am. Med.* **41**:460 (Sept.) 1935.

13. Kesten, H. D., and Silbowitz, R.: Experimental Atherosclerosis and Soya Lecithin, *Proc. Soc. Exper. Biol. & Med.* **49**:71-73 (Jan.) 1942.

14. Andrews, K. R., and Broun, G. O.: Comparison of the Action of Choline and Lipocain in the Prevention of Cholesterol Atherosclerosis in the Rabbit, *J. Clin. Investigation* **19**:786 (Sept.) 1940.

15. Gross, P., and Kesten, B.: Treatment of Psoriasis with Lipotropic Substances Derived from Foodstuffs, *Arch. Dermat. & Syph.* **47**:159-174 (Feb.) 1943.

Adlersberg and Sobotka,<sup>16</sup> employing 12 to 15 Gm. of either crude or defatted soybean lecithin daily for ten days to thirteen weeks, reported a gradual and progressive fall in the serum cholesterol in 5 patients with xanthomatosis and hypercholesteremia. Paul, Daum and Kemp<sup>17</sup> treated 1 patient with xanthomatosis (type not stated) with choline. The initial total blood fat was 2,208 mg. per hundred cubic centimeters, the phospholipids 1,364 mg. per hundred cubic centimeters and the cholesterol 660 mg. per hundred cubic centimeters. After fifteen days of choline therapy (3 Gm. daily, though the dose was not specifically stated), the total blood fat had decreased to 1,762 mg., the phospholipids to 756 mg. and the cholesterol to 425 mg. per hundred cubic centimeters. In the present study, these observations could not be confirmed. There was no sustained drop in serum cholesterol in any of the 4 patients given 18 to 54 Gm. of crude or 12 to 24 Gm. of defatted lecithin continuously for eight to fifteen weeks.

There have been several reports on the administration of lipocaic to patients with primary (essential) xanthomatosis and hypercholesteremia. Rosenak<sup>18</sup> prescribed for an adult patient 2 Gm. of lipocaic daily for two months and later increased the dose to 3 Gm. for another two months, without any effect on the hypercholesteremia. Comfort, Shepard and Snell,<sup>19</sup> using lipocaic intermittently or continuously for periods up to two weeks and in doses of 2 to 8 Gm., observed no effect on the serum cholesterol levels in an adult with xanthomatous biliary cirrhosis. In the present study there was no clinical improvement, either in the lesions or in the serum cholesterol values in an 11 year old child given 6 Gm. of lipocaic daily for twenty-four weeks and the same amount of pancreatic extract with lipocaic-like properties for the next fourteen weeks.

The decided variability of the plasma lipids in persons with primary (essential) xanthomatosis studied over long periods of time is apparent, but not real. In 2 patients investigated at repeated intervals for forty-seven and forty weeks, respectively (cases 1 and 7), the maximum

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16. Adlersberg, D., and Sobotka, H.: Effect of Prolonged Lecithin Feeding on Hypercholesterolemia, *J. Mt. Sinai Hosp.* **9**:955-956 (March-April) 1943.

17. Paul, W. D.; Daum, K., and Kemp, C. R.: The Action of Choline on the Blood Lipid Fractions in Cirrhosis of the Liver, Diabetes Mellitus and Related Conditions of Disturbed Fat Metabolism, *J. Iowa M. Soc.* **37**:146-152 (April) 1947.

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19. Comfort, M. W.; Shepard, V. D., and Snell, A. M.: Xanthomatous Biliary Cirrhosis: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **16**:374-377 (June 11) 1941.

deviation from the average blood cholesterol was less than 15 per cent (case 5, studied for fifty weeks, is omitted from these calculations because of the obvious reduction of the serum cholesterol apparently due to a diet low in fat and low in cholesterol). These observations agree with the observations recorded by several workers,<sup>20</sup> who reported remarkable constancy of the blood cholesterol of normal adults studied for long periods of time. As pointed out by Weinhouse,<sup>21</sup> the relatively wider fluctuations of the blood cholesterol in persons reported by other workers<sup>22</sup> amounted to approximately 15 per cent when recalculated as deviations from the average. It would appear, therefore, that the blood cholesterol in patients with xanthomatous disease exhibits no greater variations over periods of several months than that observed in normal persons. The apparent wider fluctuations are obviously due to higher levels of blood cholesterol.

#### SUMMARY AND CONCLUSIONS

In 7 patients with primary (essential) xanthomatosis and hypercholesteremia, the oral administration of vitamin E (d,l-alpha-tocopherol acetate or mixed natural tocopherols) failed to decrease the level of the total plasma lipids, fatty acids and cholesterol.

In 4 patients with primary (essential) xanthomatosis and hypercholesteremia, oil-free or crude lecithin likewise failed to decrease the level of the serum cholesterol.

In 1 patient with primary (essential) xanthomatosis and hypercholesteremia, the ingestion of relatively large doses of lipocaic and pancreatic extract did not diminish the level of the serum cholesterol.

In 4 patients with secondary hypercholesteremia due to various metabolic defects (e.g., diabetes mellitus), vitamin E (d,l-alpha-tocopherol acetate or mixed natural tocopherols) failed to influence the level of plasma cholesterol. In 2 of these 4 patients, there was a sustained reduction in the total plasma lipids and fatty acids without alteration in the plasma cholesterol.

The variations of the serum cholesterol in patients with xanthomatosis studied over many months were no greater than those reported for normal persons; the apparent wider fluctuations were due unquestionably to the elevated levels of serum cholesterol in patients with xanthomatous disease.

20. Sperry, W. M.: The Concentration of Total Cholesterol in the Blood Serum, *J. Biol. Chem.* **117**:391-395 (Jan.) 1937. Turner, K. B., and Steiner, A.: A Long Term Study of the Variation of Serum Cholesterol in Man, *J. Clin. Investigation* **18**:45-49 (Jan.) 1939.

21. Weinhouse, S.: The Blood Cholesterol, *Arch. Path.* **35**:438-500 (March) 1943.

22. Schube, P. G.: Variations in the Blood Cholesterol of Man over a Time Period, *J. Lab. & Clin. Med.* **22**:280-284 (Dec.) 1936. Man, E. B., and Gildea, E. F.: Variations in Lipemia of Normal Subjects, *J. Biol. Chem.* **119**:769-780 (July) 1937.



# EFFECT OF PROPHYLACTICALLY ADMINISTERED PENICILLIN ON INCIDENCE OF BACTEREMIA FOLLOWING EXTRACTION OF TEETH

Results in Patients with Healed Rheumatic and Bacterial Endocarditis

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The frequency of bacteremia following the extraction of teeth and its importance in the development of bacterial endocarditis have been established both experimentally<sup>1</sup> and clinically.<sup>2</sup> Since endocarditis is such a serious disease, the introduction of the sulfonamide compounds and antibiotics has been inevitably followed by studies to determine their value in the prevention and eradication of this bacteremia. Although the results obtained by sulfonamide prophylaxis were

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Drs. Georgine Rotman-Kavka, Jay A. Robinson, William W. Zeller and Schneider Spiegel cooperated in the completion of these studies, and Miss Joan Rowe rendered technical assistance.

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encouraging, nevertheless cases of bacterial endocarditis were observed after premedication with the sulfonamide drugs. Because penicillin is superior to sulfonamide compounds in the treatment of endocarditis, it seemed advisable to us to employ this antibiotic in an attempt to prevent the bacteremia which follows dental extraction.

#### PLAN OF STUDY

Patients who were to have teeth extracted were placed in two groups, one to receive penicillin before operation and the other to serve as a control. In nearly every instance, the patient had been admitted to one of the services of a general hospital for some other illness, and the need for dental extraction was usually incidental. All types of patients were included in the study, except that no one was included who had rheumatic or congenital heart disease or an infectious disease which was likely to be accompanied with bacteremia. There was no selection of patients according to age, color, sex, number of teeth to be extracted or condition of the gums. Patients were not included in the study if they had received a chemotherapeutic or antibiotic agent during the previous twenty-four hours.

The choice of the type and dose of penicillin and of the time of administration in relation to the time of extraction was based on several considerations. We decided to employ a preparation which could be administered simply in the private practice of a dentist or physician, and an amount which would assure a peak concentration in the blood at the time of extraction and maintain an adequate concentration for a maximum period of time. On the basis of previous work, a dose of 600,000 units of penicillin in peanut oil and beeswax<sup>3</sup> given three to four hours before extraction was selected as best satisfying those requirements.

It was our purpose to employ all of the procedures known to decrease the incidence of bacteremia and, at the same time, to utilize measures which would facilitate the growth of any bacteria that reached the blood. Accordingly, we decided to obtain local anesthesia by means of procaine hydrochloride, to which had been added epinephrine hydrochloride in a dilution of 1:25,000, employing infiltration, alone or combined with the conduction method, depending on the location of the tooth. Local infiltration anesthesia has been shown to decrease the incidence of bacteremia.<sup>2c</sup> Feldman and Trace<sup>4</sup> suggested that the use of a local anesthetic causes compression of the blood vessels and lymphatics and minimizes dissemination of any bacteria present. In rabbits, procaine is reported to increase the bactericidal and phagocytic power of the blood and thus to act both as a systemic and as a local barrier to the entrance of organisms into the circulation.<sup>5</sup> Furthermore, epinephrine, by its vasoconstricting action, decreases the possibility of the bacteria gaining access to the blood stream.<sup>2c</sup>

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3. Hirsh, H. L.; Dowling, H. F.; Vivino, J. J., and Rotman-Kavka, G.: Penicillin in Beeswax and Peanut Oil, a New Preparation Which Is Fluid at Room Temperature: Absorption and Therapeutic Use, *J. Lab. & Clin. Med.* **32**: 34, 1947. One cubic centimeter of this preparation contains 300,000 units of penicillin in refined peanut oil containing 4.8 per cent bleached beeswax, U. S. P.

4. Feldman, L., and Trace, I.: Subacute Bacterial Endocarditis Following Removal of Teeth or Tonsils, *Ann. Int. Med.* **11**:2124, 1938.

5. Villardo, S.: Immunity Phenomena in Procaine Hydrochloride Anesthesia, *Gior. di batteriol. e immunol.* **20**:1201, 1938.

Two of us (D.H.F. and H.L.H.)<sup>6</sup> have shown previously that the addition of penicillinase to culture mediums to be used for body fluids containing penicillin facilitates the growth of any bacteria present. This enzyme<sup>7</sup> was added to the culture mediums to be used for blood of the patients receiving penicillin, since preliminary tests had demonstrated that penicillinase did not influence the growth of bacteria other than by inactivating the penicillin present.

Studies by several investigators<sup>8</sup> demonstrated that the addition of sodium polyantholsulfonate ("liquoid") to culture mediums in concentrations of 0.33 to 0.2 per cent favored the growth of organisms present in the blood to be cultured. These investigators expressed the opinion that this compound impaired or destroyed the native antibody present in normal human blood. We employed "liquoid"<sup>9</sup> in the culture medium in a concentration of 0.3 per cent. It was added only to the medium employed for aerobic culture, however, inasmuch as Hoare<sup>10</sup> reported that "liquoid" is unfavorable to the growth of anaerobic streptococci.

Twenty cubic centimeters of blood was taken immediately after the extraction of the teeth, and again, ten and thirty minutes later. Eight to 10 cc. was placed in 30 cc. of culture medium for aerobic culture and an equal amount in a similar medium for culture under anaerobic conditions. In the case of patients receiving penicillin, the remainder of the blood was used for determination of the penicillin concentration. Hirsh, Dowling and O'Neil<sup>11</sup> found that these amounts were the optimal proportions for this purpose. The flasks were incubated at 37 C. Anaerobic conditions were obtained in a museum jar with a lighted candle. The culture flasks were inspected daily, but subcultures were not made for seven days unless there was evidence of growth at an earlier date. Subcultures were made on blood agar plates. Throat cultures were made on blood agar plates on all patients before extraction, and a culture was made from the tooth socket immediately after the tooth was extracted. This was done in order to discover the presence of similar strains in the blood and in the tooth socket or the pharynx. The detailed results are to be published elsewhere.<sup>12</sup>

6. Dowling, H. F., and Hirsh, H. L.: The Use of Penicillinase in Cultures of Body Fluids Obtained from Patients Under Treatment with Penicillin, *Am. J. M. Sc.* **210**:756, 1945.

7. Supplied by Schenley Laboratories, Inc.

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9. Supplied by Hoffman-La Roche, Inc., Nutley, N. J.

10. Hoare, E. D.: The Suitability of "Liquoid" for Use in Blood Culture Media, with Particular Reference to Anaerobic Streptococci, *J. Path. & Bact.* **48**:573, 1939. Reichel, H. A.: Removal of Bacteria from the Blood Stream: Experiments Tending to Determine Rate of Removal of Injected Bacteria in Blood, *Proc. Staff Meet., Mayo Clin.* **14**:138, 1939.

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12. Vivino, J. J.; Hirsh, H. L.; Dowling, H. F., and Merril, A.: Identification of Organisms Cultured in the Blood of Patients Following Dental Extraction: Correlation with Organisms Cultured from the Pharynx and Tooth Socket, to be published.

In order to evaluate whether the condition of the mouth or the type of extraction had any influence on the incidence of bacteremia, each of these factors was classified. The state of the oral hygiene of the patients was rated on the basis of the severity of dental caries and gingival disease as follows: (a) no apparent disease, (b) mild dental caries and/or gingivitis, (c) moderate dental caries and/or gingivitis and (d) presence of frank pus.

The amount of trauma which accompanied the extraction was indicated by the following operative classification:

Type

- 1 Tooth loose
- 2 Plain forceps extraction
- 3 Extraction requiring the use of elevators
- 4 Extraction requiring bone surgery

### RESULTS

Sixty-five patients were given 600,000 units of penicillin in oil and wax three to four hours before the extraction of teeth, and an equal number of patients who had teeth extracted were not given penicillin and served as controls. The two groups were essentially alike with respect to age, sex and racial distribution. On the basis of the classifications previously outlined, the oral hygiene and types of extraction were comparable for the two groups. The number of teeth extracted from the patients in the control group averaged 2.4 (range, 1 to 11), while for the penicillin-treated group the average was 3.1 (range, 1 to 14).

The varieties of organisms found and the frequency with which they were encountered for the two groups at each time interval are shown in table 1. Since in many instances the same organism was isolated both in the aerobic and in the anaerobic cultures, the total number of positive cultures for the same organism at each time interval is indicated by the figures in the third column for each group. For each time period studied the incidence of bacteremia was higher for the group of patients serving as controls than for the group receiving penicillin. For the time immediately following extraction the incidence was 25

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13. (a) Pressman, R. S., and Bender, I. B.: Effect of Sulfonamide Compounds on Transient Bacteremia Following Extraction of Teeth: I. Sulfanilamide, *Arch. Int. Med.* **74**:346 (Nov.) 1944. (b) Bender, I. B., and Pressman, R. S.: Factors in Dental Bacteremia, *J. Am. Dent. A.* **32**:836, 1945. (c) Northrop, P. M., and Crowley, M. C.: Further Studies on the Effect of the Prophylactic Use of Sulfathiazole and Sulfamerazine on Bacteremia Following Extraction of Teeth, *J. Oral Surg.* **2**:134, 1944.

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TABLE 1.—Incidence of Positive Cultures Following Dental Extraction

Organisms	Immediately After Extraction						Ten Minutes After Extraction						Thirty Minutes After Extraction					
	Control Group			Penicillin-Treated Group			Control Group			Penicillin-Treated Group			Control Group			Penicillin-Treated Group		
	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total
Alpha and gamma streptococci	17	9	19	7	4	8	5	4	7	2	1	3	1	1	2	0	0	0
Staphylococcus albus	0	1	1	2	1	3	1	3	4	3	1	4	2	1	3	2	2	4
Staphylococcus aureus	1	2	3	0	0	0	1	3	4	1	0	1	0	0	0	1	0	1
Diphtheroids	1	0	1	0	2	2	2	0	2	0	0	0	0	2	2	1	0	1
Neisseria	1	0	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0
Other organism	0	0	0	0	0	0	0	0	0	0	2	2	1	0	1	1	0	1
Total	20	12	25	9	8	14	9	10	17	6	5	11	4	4	8	5	2	7

\*Total number of different strains; some organisms were found both aerobically and anaerobically.

TABLE 2.—Number of Patients with Bacteremia Following Dental Extraction\*

Organisms	Immediately After Extraction				Ten Minutes After Extraction				Thirty Minutes After Extraction				Total Number of Cultures†				Total Number of Patients			
	Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group	
	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
All organisms	22	34	13	20	14	22	10	15	8	12	7	11	--	--	30	--	30	46	24	37
Alpha and gamma streptococci	19	29	8	12	7	11	3	5	2	3	0	0	64	37	11	37	22	34	10	15
Other organisms	6	9	6	9	9	14	8	13	6	9	7	11	21	63	21	63	9	14	16	25

\*Some patients had more than one organism in the culture at the same time.

†Positive at all three periods for different organisms (table 1: Six patients in control groups and 2 in penicillin-treated group had same organism at more than one period).

‡Percentage of total number of positive cultures.

for the control series, as compared with 14 for the penicillin-treated patients. For the ten minute interval, the number of cultures yielding pathogens was 17 and 11, and for the thirty minute interval, 8 and 7 respectively.

The total number of patients whose blood was found to contain organisms on culture is shown in table 2. For the time immediately after extraction, the number of patients with blood cultures yielding organisms was 22 (34 per cent) in the control group and 13 (20 per cent) in the penicillin-treated group. The corresponding figures for the ten minute interval after extraction were 14 (22 per cent) and 10 (15 per cent), and those for the thirty minute interval 8 (12 per cent) and 7 (11 per cent), respectively. The apparent discrepancy between the total number of positive cultures and the total number of patients having positive cultures for the first two of the intervals studied is accounted for by the fact that cultures for some patients yielded more than one organism at each of the periods studied. For all the time periods studied, 30 of 65 patients (46 per cent) in the control group were found to have bacteremia, whereas 24 of the 65 (37 per cent) treated with penicillin had bacteremia after operation. These differences are not statistically significant when tested by the chi square method.

Since the alpha and gamma streptococci are the important bacteria in the pathogenesis of bacterial endocarditis, we have divided the patients into those from whose blood alpha and gamma streptococci were isolated and those from whose blood one of the other organisms was cultured (table 2). It is obvious that the differences in favor of the penicillin-treated patients are the result of decreased incidence of bacteremia due to the alpha and gamma streptococci. The incidence of bacteremia for the other organisms was essentially the same for the two groups of patients. When alpha and gamma streptococci alone are considered, the differences between the incidence of bacteremia for the penicillin-treated group and that for the control group for the period immediately following extraction is statistically significant when tested by the chi square method, whereas the differences at the other two periods studied are not statistically significant. The difference between the number of patients (22, or 34 per cent) with bacteremia at any time due to the alpha and gamma streptococci in the control group as compared with the number (10 or 15 per cent) in the penicillin-treated group is also statistically significant. It appears likely, therefore, that penicillin was instrumental in decreasing the incidence of bacteremia due to streptococci but not that due to the other organisms.

In addition to the incidence of bacteremia, the persistence of the various strains isolated was determined. It was found that 6 patients in the control group had positive cultures for the same strain at more

than one time interval, whereas this occurred for only 2 patients in the penicillin-treated group. Because of the small number of cases, this difference is not statistically significant.

An attempt to correlate the incidence of bacteremia in the two groups of patients according to age, sex, race and condition of the gum and teeth revealed no relation of these factors. When the type of operation is considered, a definite increase in the incidence of bacteremia in the more extensive surgical procedures is apparent for both the penicillin-treated and the control group of patients. In the penicillin-treated group, none of the patients with type 1 or 4 extraction had bacteremia. The incidence of bacteremia for extractions of types 2 and 3 was 31 per cent in each group. None of the patients in the control group with a type 1 extraction had bacteremia. Of the patients with extractions of types 2, 3 and 4, 36, 59 and 40 per cent, respectively, had bacteremia. The increase was noted for both the alpha and the gamma streptococci, as well as for the other organisms isolated. It is apparent that penicillin reduced the incidence of bacteremia following more extensive surgical procedures.

In those patients treated with penicillin from whose blood cultures organisms were isolated at any period, the concentration of penicillin in the blood was determined for that period. In addition, the in vitro sensitivities of most of the bacteria isolated were determined. In the case of the alpha and gamma streptococci, the concentrations of penicillin in the blood were always greater than the in vitro sensitivity of these organisms. Of the other organisms, about one-half were sensitive to less and the others resistant to more than the penicillin concentration present in the blood at the time interval at which they were found. None of the patients in this series had any complications as a result of the dental extractions other than the transient bacteremia.

#### PATIENTS WITH HEALED ENDOCARDITIS

Seven patients with rheumatic or healed bacterial endocarditis were given penicillin before the extraction of teeth on 11 occasions. These patients were not included in the series because they represented cases specially selected for penicillin therapy. In the case of 4 of the extractions, the patients received 25,000 units of penicillin one hour before extraction and 25,000 units every three hours thereafter, for seven doses. In the remaining 7 extractions, 600,000 units in 2 cc. of oil and wax was given three to four hours before the extraction. In 4 instances, bacteria were cultured from the specimen of blood taken immediately after extraction. In 3 instances the organism was *Streptococcus viridans* (alpha type) and in the fourth *Staphylococcus albus*. All of

these patients made an uneventful recovery and have been followed for periods of from six months to two years. The strain of *Staph. albus* and one of the strains of *Str. viridans* were sensitive to less penicillin than was found in the blood at that time, while the other two strains were resistant to the concentrations present in the blood.

#### COMMENT

The desirability of eliminating, or even diminishing, the frequency of one of the causes of bacterial endocarditis is obvious. The effect of sulfonamide prophylaxis on the incidence and persistence of bacteremia following the extraction of teeth has been inconclusive. Some reports have indicated that sulfonamide compounds were ineffective, while other investigators<sup>13</sup> have stated that these drugs either decreased the incidence of bacteremia or caused a prompter disappearance of the organisms from the blood. Not only are the reports contradictory, but it is difficult to evaluate the results adequately, as in most of the series either there was no control group or the investigators failed to include para-aminobenzoic acid in their culture mediums. The necessity for the use of para-aminobenzoic acid in the culture mediums to be used for body fluids containing sulfonamide drugs has been established.<sup>14</sup> Furthermore, the fact that sulfonamide compounds under most conditions are only bacteriostatic would make it appear unlikely that these drugs could effect a more rapid disappearance of organisms from the blood over a ten minute period than has been reported.<sup>13a, b</sup>

The present study was undertaken to evaluate the use of penicillin before dental extraction. We gave penicillin prophylactically to 65 unselected patients and observed the incidence of bacteremia after tooth extraction in these patients as compared with the control group of 65 patients who were not given penicillin. When all the organisms cultured from the blood are considered, it is apparent that penicillin did not significantly reduce the incidence of bacteremia. It should be noted, however, that only 53 per cent of all the organisms isolated were alpha and gamma streptococci. The incidence of organisms other than alpha and gamma streptococci is higher than most investigators have reported. We are of the opinion that these organisms were actually present in the blood. Similar organisms were frequently isolated from the cultures made from the throat and tooth sockets, and it is conceivable that they, as well as the alpha and gamma streptococci, could gain access to the blood through the open wound. All the specimens of blood were obtained by 4 persons, and strict measures were observed for minimizing contamination. Furthermore, in the course of routine work done concomitantly in the same laboratory, hundreds of cultures of blood



taken by numerous persons under less ideal conditions were examined. In all these cultures the number of bacteria obtained as contaminants was exceedingly low. In any event, the organisms other than the alpha and gamma streptococci isolated from the blood cultures are of little significance in the pathogenesis of bacterial endocarditis.

If alpha and gamma streptococci alone are considered, it is observed that 600,000 units of penicillin in wax and oil, given three to four hours before dental extraction, reduced the incidence of bacteremia for the penicillin-treated patients as compared with that for the controls immediately after extraction and ten and thirty minutes later. The decreases for the period immediately after extraction and for the total number of patients who had bacteremia at any time were statistically significant.

Glaser and his associates<sup>15</sup> recently reported a study similar to ours in which 40 patients were given large doses of penicillin over a twenty-four hour period before extraction and an equal number served as controls. Blood was taken for culture before and immediately after extraction. Sixty per cent of the patients were found to have alpha or gamma streptococci in the postextraction culture, whereas the incidence was only 40 per cent in the penicillin-treated group. In the control group the alpha streptococci predominated, whereas in the penicillin-treated group the gamma streptococci were found more frequently. In patients with normal gums the use of penicillin did not result in a significant decrease in the incidence of bacteremia after the extraction of teeth. On the other hand, in the patients with gingivitis or pyorrhea the dosage schedule of penicillin employed resulted in a definite decrease in the incidence of bacteremia. These investigators concluded that in patients with rheumatic or congenital heart disease penicillin should be given in large doses for at least twenty-four hours before extraction and should be continued for two to three days thereafter. In patients with normal gums the penicillin may be given before extraction and continued for the same period.

It is interesting to speculate how penicillin prevents the bacteremia following dental extraction. There appear to be two possible explanations. One is that the presence of penicillin in the blood inhibits or kills the organisms after they enter the blood. The other explanation is that penicillin inhibits the growth of bacteria in the gums and in the mouth and throat and thus reduces the number of organisms available for entrance into the blood through the wound. It is probable that both mechanisms operate. A diminution in the number of bacteria in the vicinity of the wound by the use of penicillin before extraction would explain the lower percentage of bacteria present immediately after extraction among the patients who received this antibiotic prophylactically.

This mechanism might also explain the rapid disappearance of the bacteria which entered the blood, since it may be presumed that when bacteria gained access at all they were present in smaller numbers. On the other hand, it is quite likely that the penicillin present in the blood inhibited their multiplication and thus contributed to their rapid disappearance. Unfortunately, we did not make pour plates to determine the number of organisms present in the blood.

Since the bacteremia following dental extraction is of such importance, we believe that certain principles in the management of patients with known rheumatic or congenital heart disease contemplating dental extractions are worthy of emphasis. Patients who are to have extractions should be questioned carefully concerning a previous history of rheumatic fever, chorea, joint pains, growing pains, unexplained periods of fever, frequent sore throats, scarlet fever or any manifestation of a rheumatic diathesis. In the presence of a suggestive, and certainly with a definite, history of rheumatic fever, the patient should be examined for the presence of valvular heart disease before having the dental work undertaken. Patients with a history of cardiac difficulties, such as dyspnea or cyanosis, indicative of congenital heart disease should be similarly managed.

The present study, in conjunction with that of Glaser and his associates, indicates that the incidence of bacteremia caused by alpha and gamma streptococci can be significantly reduced by the use of penicillin before extraction. The optimal dose and time of administration remain to be worked out. On the basis of present knowledge, it seems to us, that the best procedure would be one that assured the presence of penicillin in the gums and adjacent tissues for twenty-four hours before extraction, a peak concentration of penicillin in the blood during and immediately after the extraction and a bactericidal concentration in the blood for at least twenty-four hours after extraction. A practical program which would accomplish this objective would consist of an injection of 300,000 units of penicillin in wax and oil (or a similar preparation) about twenty-four hours before extraction was contemplated. Three to four hours before the extraction an additional dose of 600,000 units of penicillin in wax and oil should be administered.

On the basis of previous investigations, extractions performed by simple elevator-forceps technic, with local infiltration anesthesia induced with procaine and epinephrine, offer the best means of reducing the incidence of bacteremia. Although we were unable to correlate the incidence of bacteremia with the number of teeth extracted, there was a definite correlation between the severity of the surgical procedure and the incidence of bacteremia. Therefore, in patients with rheumatic and congenital heart disease, any manipulative procedure involving the gums and teeth is to be avoided if possible.

## SUMMARY

Sixty-five patients requiring dental extractions were each given 600,000 units of penicillin in wax and peanut oil contained in 2 cc. of the mixture three to four hours before extraction, while 65 patients were not given penicillin and served as controls. Extraction was accomplished by the elevator-forceps technic, local infiltration anesthesia being induced with procaine and epinephrine. Blood cultures in duplicate were obtained immediately and ten and thirty minutes after extraction, incubated both aerobically and anaerobically and studied for the presence of bacteria.

When all the organisms isolated were considered, 46 per cent of the patients in the control group and 37 per cent of the patients in the penicillin-treated group were found to have bacteremia. When alpha and gamma streptococci alone were considered, a statistically significant reduction in the incidence of bacteremia, from 34 to 15 per cent, was observed with the use of penicillin.

Six patients in the control group had positive cultures for the same organism at more than one of the periods studied. Only 2 patients in the penicillin-treated series had bacteremia at more than one period.

The incidence of bacteremia could not be correlated with age, sex, race, state of oral hygiene or number of teeth extracted. The number of positive cultures was greater, however, the more extensive the surgical procedure.

Seven patients with healed rheumatic or bacterial endocarditis had dental extractions on 11 occasions, with penicillin administered prophylactically. A transient bacteremia occurred in 4 patients.

A plan of prophylaxis is suggested for use preceding dental extraction in patients with rheumatic and congenital heart disease.

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# ADDISON'S DISEASE COMPLICATED BY TOXEMIA OF PREGNANCY

Review of the Literature

MONROE COHEN, M. D.

BROOKLYN

Before the discovery of potent adrenal cortex preparations, the maternal mortality in Addison's disease complicated by pregnancy was 35 per cent among the 20 reported cases. Some case reports are brief, but in most instances the diagnosis of adrenal disease was proved at autopsy. Therapeutic abortions were uniformly fatal, and one third of the fetuses died at term delivery.<sup>1</sup>

From 1930 to 1939, 8 cases, with a 25 per cent mortality, were reported. In 4 cases the pregnancies went to term and the patients survived, and in 2 cases therapeutic abortions were successful. Uncontrollable vomiting leading to adrenal crisis caused the death of 1 patient in the second month of pregnancy, and premature labor terminated in the death of another.<sup>2</sup>

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From the Department of Medicine, Long Island College of Medicine Division, Kings County Hospital.

1. Davey, N. F.: Case of Complete Disorganization of Both Supra-Renal Capsules Without Discoloration of the Skin, *M. Times & Gaz.* **18**:30, 1859. von Roten, J.: Kasuistik zur Frage des Morbus Addisonii und Gravidität, Inaug. Dissert. (Basel), Sarnen, L. Ehrli, 1915. Fitzpatrick, G.: Addison's Disease Complicating Pregnancy, Labor or the Puerperium, *Surg., Gynec. & Obst.* **35**:72, 1922. Fruhinsholz, A.: Fatal Suprarenal Syndrome of the Addisonian Type Connected with the Puerperal Condition, *Gynec. et obstét.* **12**:437, 1925. Gustafsen, P., cited by Crabtree, E. G.: *Urological Diseases of Pregnancy*, Boston, Little, Brown & Company, 1942, p. 369.

2. Garcia, F. H.: Pregnancy and Addison's Disease, *Med. ibera* **2**:391, 1931. Perkins, P. A.: Addison's Disease and Pregnancy, *J. A. M. A.* **99**:1500 (Oct. 29) 1932. Bachner, F.: The Problem of Interruption of Pregnancy in Addison's Disease, *Zentralbl. f. Gynäk.* **56**:1039, 1932. Tapfer, S.: Pregnancy and Addison's Disease, *Wien. klin. Wchnschr.* **47**:1043, 1934. Thaddea, S.: Relationships Between Adrenal Cortex and Sex Glands, *Ztschr. f. Geburtsh. u. Gynäk.* **110**:225, 1935. Eng, H.: Fluctuation Between Sex Hormones and Other Endocrine Organs: Secretion of Sex Hormones in a Patient with Adrenal Insufficiency, *Klin. Wchnschr.* **14**:6, 1935. Stohr, R.: Addisonism in Pregnant Women, *Zentralbl. f. Gynäk.* **63**:2599, 1939.

Since 1940 there were 15 reported cases, and 7 more have been available to us for study. In 18 of the 22 cases the pregnancy went to term, with 2 deaths. The fact that both deaths occurred in Brooklyn and were unreported makes it likely that few fatal cases are being reported. One of the patients died of a ruptured uterus during a low forceps delivery.<sup>3</sup> The other survived cesarean section and died of acute pulmonary edema on the third day.<sup>4</sup> Therapeutic abortions terminated the pregnancy in the remaining 4 cases; 2 of the patients died, 1 of septicemia and the other of adrenal crisis. The total mortality in this period was 18 per cent. Only 3 fetal deaths after term deliveries are mentioned since 1930, and 2 were unrelated to Addison's disease (tables 1 and 2).

The case here reported is the first to be complicated by preeclamptic toxemia; both mother and child left the hospital in excellent health.

#### REPORT OF A CASE

A 17 year old white school girl was admitted to the Kings County Hospital in June 1940 because of diffuse abdominal pain, vomiting, anorexia, considerable asthenia, a loss of weight of 30 pounds (13.6 Kg.) and pigmentation of the skin. She appeared extremely ill. The blood pressure was 74 systolic and 40 diastolic, and there was pronounced pigmentation of the skin and the mucous membranes. Roentgenologic study of the chest revealed small exudative tuberculous lesions at both apexes. She responded to infusions of isotonic sodium chloride solution, but later suffered a typical addisonian crisis during a chloride excretion test. After a stormy course, she was eventually given a house diet with 6 Gm. of added salt and 5 mg. of desoxycorticosterone acetate daily. She did well on this regimen, gradually gained weight and maintained a blood pressure of 120 to 130 systolic and 70 to 80 diastolic. Study of the lungs at intervals disclosed stationary and inactive lesions. In November 1940, 5 pellets of 125 mg. of desoxycorticosterone acetate were implanted in the patient. Seven months after her admission she was discharged from the hospital in good condition, having gained 26 pounds (11.8 Kg.). There was a tendency toward edema formation, and the salt in the diet was restricted.

Because of loss of weight and the fall in blood pressure, 5 pellets of 50 mg. of desoxycorticosterone were implanted in August 1942. In December 1943, 3 pellets of 125 mg. were implanted after the patient's condition had been well controlled with the administration of 3 mg. daily. Four pellets of 125 mg. were implanted on June 1, 1945, and except for mild edema of the hands and feet for several months she felt well.

Complaining of weakness and nausea of one week's duration, the patient was readmitted to the hospital on Feb. 19, 1946, when it was learned that her last normal menstrual period had occurred on Dec. 19, 1945. Examination revealed a six week intrauterine gestation. The blood pressure was 100 systolic and 68 diastolic, the hemoglobin 12.5 Gm. per hundred cubic centimeters and the white blood cell count 8,000, with a normal differential count. The urine was normal,

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3. Unreported case, Cumberland Hospital, 1941.

4. Unreported case, Long Island College Hospital, 1946.

the blood sugar was 92 mg. per hundred cubic centimeters and the uric acid 3.9 mg. A roentgenogram of the chest showed calcific deposits in the right lower pulmonary fields. Adrenal studies showed no calcification. With control of diet, infusions of dextrose and sodium chloride and adrenocortical therapy, the nausea and vomiting disappeared and the patient was discharged to the antepartum clinic.

TABLE I.—*Cases of Addison's Disease and Pregnancy Since 1940*

Date	Author	Comment
1941	Unreported <sup>a</sup>	Death during delivery from ruptured uterus; low forceps used; stillbirth; atrophic adrenals at autopsy
1943	Samuels, L. T.; Evans, G. T., and McKelvy, J. L.: <i>Endocrinology</i> 32:422, 1943.	Uneventful pregnancy; symptoms of Addison's disease returned after delivery; 17-ketosteroids rose in last trimester
1945	Sheldon, D. E.: <i>Am. J. Obst. &amp; Gynec.</i> 42:269, 1945.	Term delivery; mother and infant survived; moderate adrenal crisis on third day
1945	Van Zwanenberg, J.: <i>St. Barth. Hosp. J.</i> 49:31, 1945.	Survival of 1 patient after term delivery; another patient died 3 days after hysterotomy and sterilization at the fourth month
1946	Valenzi, A.: <i>Clin. obstet.</i> 38:459, 1946.	Normal delivery at term, with live baby; death in 2 months, not associated with pregnancy; autopsy revealed Addison's disease
1946	Murphy, A. P.: <i>Proc. Roy. Australasian Coll. Phys.</i> 1:69, 1946.	Labor induced as patient was 3 weeks past term; easy, rapid, uneventful labor; stillbirth due to cord loops around neck
1946	Simpson, S. L.: <i>Proc. Roy. Soc. Med.</i> 39:511, 1946.	Two pregnancies without complications in 1 patient; survival of both infants
1946	Unreported <sup>d</sup>	Death from acute pulmonary edema on third day after cesarean section; live baby
1946	Cohen, M.	Survival of mother and baby after complication of preeclampsia
1947	Thorn, G. W.; Dorrance, S. S., and Day, E.: <i>Ann. Int. Med.</i> 16:1053, 1942.	4 patients have had six term pregnancies, with favorable outcomes. Adrenal insufficiency developed in 1 during pregnancy, crisis was precipitated by delivery in 2, and pigmentation increased in 2 after termination of the pregnancy; 1 patient died of septicemia after a therapeutic abortion. No toxemia or hypertension in any case.
1947	Loeb, R. F.: Personal communication to the author.	Of four pregnancies, one was uneventful. Hypertension developed in 1 patient in the last two months of pregnancy, without significant albuminuria, and was attributed to excess desoxycorticosterone acetate and salt; infant died of unrelated condition. One hysterectomy was done in the fifth month for reasons unrelated to the Addison's disease. One pregnancy was terminated at the second month because of recurrent hypoglycemia. All patients survived.

However, the symptoms returned, and the patient lost weight, and she was readmitted to the hospital on April 2, 1946. She was given 3 Gm. of salt daily, added to a regular diet, and 2 mg. of desoxycorticosterone acetate intramuscularly, for the pellets were beginning to lose their effect. The serum sodium content was 324 mg. per hundred cubic centimeters, potassium 19 mg., chloride 590 mg., sugar 61 mg. and the hemoglobin content 9 Gm. It was found necessary to increase the daily injections of desoxycorticosterone to 5 mg., for on this dosage the patient's condition appeared well balanced, and she gained an average of 1 pound (0.5 Kg.) per week and maintained a blood pressure of 100 to 110 systolic and 60 to 65 diastolic. The hematocrit value ranged from 32 to 35, the hemoglobin rose to 11 Gm. and chemical studies of the blood showed little change. The blood protein content was 5.7 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.8. Severe postural hypotension was present, which improved with elevation of the head of the bed and with avoidance of sudden changes in posture. After her discharge from the hospital in June, medication was given and the weight and blood pressure were taken daily by a visiting nurse and weekly at the clinic.

With an estimated date of confinement for Sept. 26, 1946, the patient was readmitted on September 5 for closer observation. Her general condition was good; the blood pressure was 124 systolic and 90 diastolic, the weight 125½ pounds (57 Kg.), the urine normal and the hematocrit value 34.

TABLE 2.—*Maternal Mortality in Addison's Disease and Pregnancy*

Date	Number of Pregnancies	Deaths			Mortality Due to Pregnancy%
		Before Term	At Term or During Puerperium	Weeks or Months After Puerperium*	
1859 to 1930	20	4	3	7	.35
1931 to 1939	8	2	0	0	.25
1940 to 1947	22	2	2	1	.18

\*These figures are not included in the statistics on mortality due to pregnancy.

On September 22 the blood pressure rose to 138 systolic and 80 diastolic and fluctuated between 120 and 135 systolic and 90 and 106 diastolic for the next week. A mild pitting edema of the feet, ankles and hands developed, associated with albuminuria (3 plus) and a gain of 3½ pounds (1.5 Kg.) in weight. The dosage of desoxycorticosterone was reduced and finally discontinued and the salt intake limited to 3 Gm. daily. After an initial dose of 30 cc. of adrenal cortex extract (Upjohn), 5 cc. of lipoadrenal extract (Upjohn) was given daily. The blood protein content was 5.2 Gm., the serum albumin 3.1 Gm., the globulin 2.1 Gm. and the uric acid 3.8 mg. per hundred cubic centimeters. The urinary 17-ketosteroids measured 3.6 mg. in twenty-four hours while the patient was on this regimen.

During the next two weeks the blood pressure ranged between 130 and 144 systolic and 90 and 104 diastolic, the edema persisted and the weight increased by 3 pounds (1.3 Kg.). The urinary albumin level reached 4 Gm. in twenty-four hours, and the fundi showed arteriovenous nicking. From October 16 to 19 aqueous adrenal extract was given to conserve the supply of lipoadrenal extract (chart 1).

Because of no evidence of the onset of labor and of the persistence of the toxemia it was decided to induce labor by rupturing the membranes and giving alphahypophamine in 1 minim doses on October 19. After the onset of fairly strong contractions, the blood pressure remained at approximately 150 systolic and 105

diastolic. Sixteen hours later it rose to 170 systolic and 120 diastolic and then to 188 systolic and 128 diastolic during contractions. Five per cent dextrose in water was given slowly intravenously. The cervix became fully dilated eighteen hours after the rupture of the membranes, and under local anesthesia an episiotomy was performed and low forceps delivery of an 8 lb. 4 oz. (3.7 Kg.) living male infant in good condition was effected. The blood loss was 500 cc. Within twenty minutes after delivery the blood pressure fell to 126 systolic and 106 diastolic and the pulse rate rose to 140. Two hundred and fifty cubic centimeters of plasma was given rapidly, and the pressure rose to 145 systolic and 105 diastolic and the pulse fell to 94. Five cubic centimeters of lipoextract was given and during the next twelve hours 1,500 cc. of 5 per cent dextrose in water. The patient remained in fair condition.

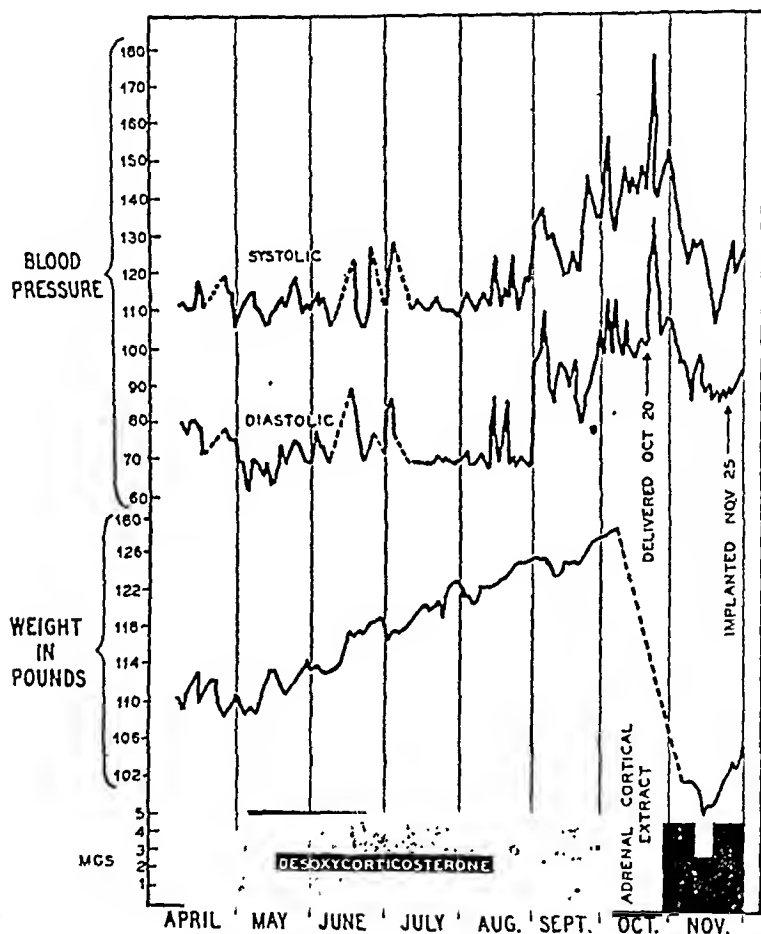


Chart 1.—Blood pressure, weight and therapy during pregnancy and puerperium in patient with Addison's disease.

During the next three days, the patient received 2 to 2½ liters of 5 per cent dextrose in water and 5 cc. of lipoadrenal extract daily with a diet containing 3 to 5 Gm. of salt. There was a decided diuresis immediately after delivery, and thereafter the urinary output exceeded the fluid intake. The hematocrit reading gradually fell to 24 and the hemoglobin to 6.5 Gm. per hundred cubic centimeters by the third day, and two blood transfusions of 500 cc. each were given on the third and fifth days, which brought the hemoglobin level to 10.5 Gm. and the hematocrit reading to 31. Blood pressures ranged between 154 and 132 systolic and 106 and 94 diastolic, the edema disappeared and the urinary albumin level



decreased to 1 or 2 plus. One week after delivery hormone therapy was discontinued, but it was reinstituted after two days when the patient suddenly became weak. She was given an infusion of sodium chloride solution, cortical extract and desoxycorticosterone, and she improved (chart 2).

After this episode 5 mg. of desoxycorticosterone was given daily, with the patient on a regular diet and 3 Gm. of extra salt. After ten days the blood pressure ranged between 110 and 120 systolic and 74 and 84 diastolic, with a hematocrit value of 38 and a hemoglobin content of 13 Gm. The dose of desoxycorticosterone was reduced to 3 mg., but after one week's trial it was raised to 5 mg. again as

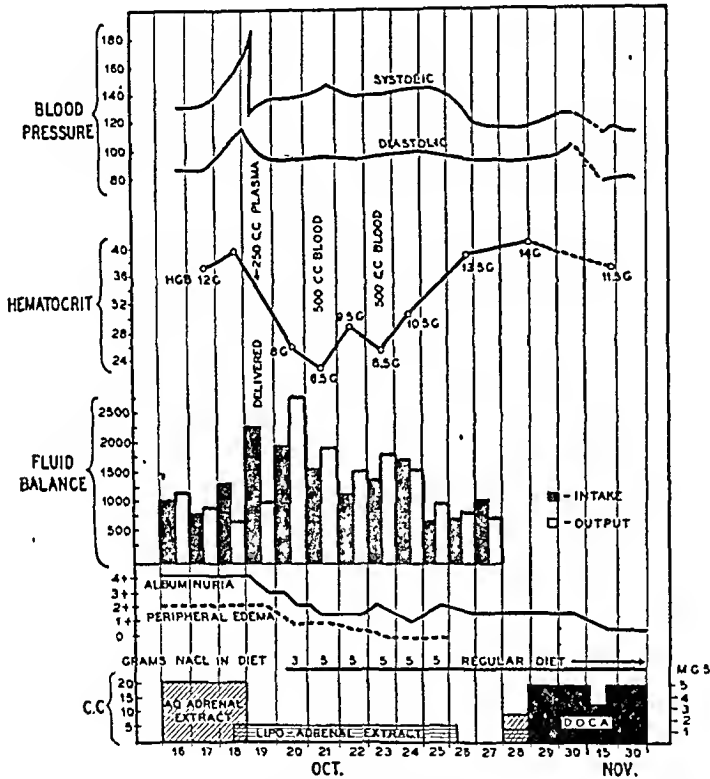


Chart 2.—Blood pressure, hematocrit reading, hemoglobin content, fluid balance, edema, albumin level and therapy at time of delivery and during puerperium.

the patient lost 4 pounds (1.8 Kg.) in weight, and the blood pressure fell to 96 systolic and 74 diastolic. With the latter dosage, the patient felt well and maintained a blood pressure of 108 to 122 systolic and 78 to 84 diastolic (chart 1).

One month after delivery she was discharged from the hospital, after implantation of 4 pellets of desoxycorticosterone acetate of 125 mg. each. The urine continued to have a trace of albumin. The hematocrit value was 37, the hemoglobin 11.5 Gm. per hundred cubic centimeters and the blood pressure 122 systolic and 84 diastolic. The baby was also discharged in good condition, appearing normal in all respects. One year later the patient and the baby were living and well.

#### COMMENT

Preeclampsia in Addison's disease has not been reported. The diagnosis in this case was established when hypertension, edema and sig-

nificant albuminuria occurred which did not change after administration of desoxycorticosterone was stopped. The salt intake had to be restricted to 3 Gm. daily, and whole extract was given. Labor was induced because of the prolonged toxemia, with risk of permanent renal damage. The mechanism of toxemia is obscure, but it is of interest that it can occur in the presence of poorly functioning adrenal glands. In this case, the amount of desoxycorticosterone acetate required formerly was relatively low, 3 pellets of 125 mg. having kept the patient well for almost eighteen months two years before her pregnancy. However, 4 pellets of 125 mg. implanted six months prior to the patient's pregnancy lasted ten months, and it is believed that this patient's adrenals produced almost no sterone since the 17-ketosteroid content was low and the amount of desoxycorticosterone acetate required during pregnancy and after delivery was 5 mg. per day. None was given from the onset of toxemia until the blood pressure fell ten days after delivery.

In a consideration of the hazards of pregnancy complicating Addison's disease, it may be noted that the normal pregnant woman has a tendency to have hypoglycemia. In the presence of Addison's disease, when carbohydrate metabolism is more impaired, there is reason for concern when there is hyperemesis in the first trimester. It is often difficult to prevent severe hypoglycemic states and adrenal crisis. Excessive vomiting requires adequate sodium chloride solution, dextrose and hormone therapy. Whole gland extract and frequent high carbohydrate feedings may control hypoglycemic episodes. Since term pregnancy offers a more favorable prognosis than therapeutic abortion, the patient should be allowed to go through the early phase of pregnancy unless some unusual or hazardous complication arises.

It has been stated that patients with Addison's disease tolerate the later months of pregnancy well because of the cortin-like action of the sex hormones, whose titer rises considerably as pregnancy advances. Their sodium-retaining action, especially that of progesterone, has been well demonstrated by the prolonged survival of adrenalectomized animals during pregnancy and heat without the use of cortical hormone. A striking and extended fall in excretion of sodium occurs in normal dogs given progesterone or estradiol.<sup>5</sup>

The fetal adrenals have been credited with supplying adrenal hormones for the maternal welfare. Houssay has recently demonstrated that the adrenals of the litter of adrenalectomized rats weigh more than those in the litter of normal mothers. Atrophy of the fetal adrenals did not occur when the mothers were given large doses of

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5. Thorn, G. W., and Harrop, G. A.: Sodium-Retaining Effect of Sex Hormones, *Science* **86**:40, 1937.

desoxycorticosterone.<sup>6</sup> However, studies on the adrenal corticoids, the fractions related to carbohydrate metabolism, show them to be increased in the first and last months of normal pregnancy. Since the infant's urine during the first few days after birth shows no corticoid activity, it is doubtful that the fetal adrenals contribute to the maternal hormone requirements.<sup>7</sup>

Most patients with Addison's disease do well after the early months of pregnancy. Pigmentation often appears lighter, and the general condition is good in the large majority as the pregnancy goes on to term. During this time the blood pressure, weight and hematocrit value are probably the most important signs to follow. Implantation of pellets is contraindicated, for the hormonal requirements might change in the last few months.

The danger of adrenal crisis is ever present during labor and the puerperium, for the loss of blood during delivery, the sudden deprivation of the sex hormones, the excretion of salt with excessive sweating during labor and the changes in blood volume with postpartum diuresis all combine to form an unpredictable, fluctuating physiologic state. Laboratory tests are of little value in these circumstances, and the clinical condition of the patient is the best guide to therapy. Adrenal cortex extract is given when labor starts and continued until the patient is well out of danger. Adequate intake of dextrose will prevent hypoglycemic reactions. Delivery should be from below, with local anesthesia, episiotomy and forceps to hasten the second stage of labor. Sodium chloride solution is needed if the labor is prolonged and sweaty and blood if appreciable hemorrhage occurs. Implantation of pellets is contraindicated until at least one month after delivery.

#### SUMMARY

1. Before 1930, 35 per cent of reported cases of pregnancy in Addison's disease resulted in maternal death before the end of the puerperium. In the 8 reported cases between 1930 and 1940 the maternal mortality was 25 per cent.

In a series of 22 cases of pregnancy in Addison's disease reported in the literature or from stated sources since 1940, only 4 deaths occurred during pregnancy and the puerperium, a mortality of 18 per cent. There were four operative interruptions in this series, accounting for 2 deaths. One death was due to uterine rupture during delivery and 1 occurred

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6. Houssay, B. A.: The Influence of Suprarenal Insufficiency on, Mother and Fetus During Pregnancy, *Rev. Asoc. méd. argent.* **60**:83, 1946.

7. Venning, E. H.: Adrenal Function in Pregnancy, *Endocrinology* **39**:203, 1946.

from pulmonary edema three days after cesarean section and liberal infusions of sodium chloride solution. No death due to crisis occurred in 16 cases in which the pregnancy went to term.

3. More careful obstetric management may further decrease the mortality from pregnancy in Addison's disease.

4. Toxemia of pregnancy may occur in Addison's disease in the absence of effective depots of desoxycorticosterone acetate in the body. Restriction of salt intake, administration of cortical extract and discontinuance of the use of desoxycorticosterone were effective therapeutic measures in the reported case until ten days after delivery, when acute symptoms of Addison's disease recurred. The amount of desoxycorticosterone acetate required after pregnancy seemed slightly greater than that required during the previous five years of the patient's disease.

The Obstetrical Department, Long Island College of Medicine Division, co-operated in the study and in the reporting of this case, and Dr. Andrew M. Babey supplied several references to case reports not cited previously.

## Book Reviews

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**Cor pulmonale: I. Congreso Nacional de Cardiología, II. Ponencia.** By J. Codina-Altés, M.D. Pp. 206, with 72 illustrations. Madrid: Libreria Editorial, Científico Médica Española, 1944.

This book is an exhaustive study of cor pulmonale, with references to all American literature but which include British, French and German references. In addition to a well organized and excellent condensation of the literature, Dr. Codina-Altés includes his personal observations on 97 cases.

The author discusses the subject in respect to etiology, pathogenesis, clinical, radiologic and electrocardiographic findings, clinical course, diagnosis and treatment and includes separate discussions of acute and subacute cor pulmonale. Charts and roentgenograms from many of his own cases are appended.

**The Management of Obesity.** By Louis Pelner, M.D. Price, \$3. Pp. 144. New York: Personal Diet Service, 1946.

In this book both the endocrine aspects of obesity and the practical management of the condition of the obese patient are discussed. Many physicians do not agree with Engelbach's classification of the hypogonad, castrate, adiposogenital and pituitarothyroid types of obesity. Not all physicians will agree with the statement that "The patient should always be given a diet consisting of about 1,000 calories," since many physicians prescribe diets containing fewer calories.

Considerable attention is given to the use of drugs in the treatment of obesity. The food tables and outlines of diets consisting of 1,000, 1,200 and 1,500 calories are satisfactory. This small volume with references and index will be helpful to many physicians.

**Recent Advances in Clinical Pathology.** By S. C. Dyke, M.D. and others. Price, \$5.50. Pp. 468. Philadelphia: The Blakiston Company, 1947.

It has become increasingly difficult for any one person to present adequately the advances in the various aspects of clinical pathology. In preparing this text on the "recent advances in clinical pathology," sponsored by the European Association of Clinical Pathologists, the editor has enlisted the aid of section editors for the four divisions of bacteriology, biochemistry, hematology and histology. These in their turn have secured the services of those best fitted to present the advances in each of their special fields. The result has been a compact but comprehensive volume, of great value not only to clinical pathologists but also to practicing physicians.

**Essentials of Medicine.** By Charles P. Emerson Jr., M.D., and Jane Elizabeth Taylor, R.N. Fifteenth edition. Price, \$3.50. Pp. 688. Philadelphia: J. B. Lippincott Company, 1946.

The appearance of a fifteenth edition of this standard work indicates that many generations of instructors in schools of nursing have found it to be a satisfactory textbook. Economy in print and margins now makes it possible to condense an immense amount of information in an octavo volume. The general format and the many diagrams, photographs and colored plates are excellent features, and we have no doubt that the book will continue to be a leader in the field of nursing education.

**Methods of Diagnosis.** By Logan Clendening, M.D., and E. H. Hashinger, M.D. Price, \$12.50. Pp. 868, with 143 illustrations. St. Louis: The C. V. Mosby Company, 1947.

Dr. Logan Clendening was a talented physician. Among other gifts he had an ability to express his ideas in writing picturesquely, entertainingly and with great vividness. He must have done his full share in the preparation of this book, for his personality and literary style are impressed on many of its pages.

The volume is divided into two distinct parts. The first deals with methods of clinical diagnosis and the second with laboratory and other special procedures.

The latter part is fairly orthodox and is a well balanced text which meets ordinary standards. The first part is more interesting because here Dr. Clendening's personal touches are so apparent. He attempts to tell any medical student or physician how to make a diagnosis: first by analysis of what the patient says, next by physical examination—and its proper technic is described carefully—and finally by the correct interpretation of what the laboratory may reveal. Fitted into this general pattern to give it color are bits of medical history, anecdotes, a great deal of common sense and a lot of clinical information based on experience. On the whole, therefore, one is likely to read the chapters in this part of the book not only for the information which they contain but also because their perusal is an enjoyable experience in medical literature.

The illustrations, in part diagrammatic and in part photographic, are excellent. The words "I" and "my" appear frequently, and many statements are dogmatic. This introduces a personal element, which is not unpleasant; one feels as if Dr. Clendening had prepared each chapter for one's special benefit.

Here is an unusual textbook. Only a rare reader will find it tedious.

**Quimioterapia antiinfecciosa en medicina interna (sulfamidas-penicilina).**

Presented at the second Congress of the Society of Internal Medicine in Argentina, October 1944. Pp. 497. Buenos Aires: "El Ateneo," 1945.

This book is a collection of papers on the subject of anti-infectious chemotherapy in internal medicine, presented in October 1944 before the Society of Internal Medicine of Buenos Aires on the occasion of its second congress. Among the numerous authors contributing to this work are well known authorities of Argentina, Uruguay, Brazil and the United States.

The first group of papers was presented at the congress and includes an introduction to the pharmacology of the sulfonamide compounds. This portion is devoted to the uses of the latter in the following infectious processes: acute and chronic respiratory diseases, septicemia, generalized infections of gynecologic or obstetric origin, rheumatic fever and pericardial conditions, nephropathies and urinary infections. Considerable mention is made of the pharmacologic qualities of penicillin and the clinical observations on its use.

The second group of papers includes discussions of the chemotherapeutic treatment of bacterial asthmas and actinomycosis and of the clinical uses of tyrothricin. Studies are presented on the analgesic and anesthetic properties of sulfathiazole. These papers were communicated to the meeting and not read before it.

Some of the concepts presented have changed greatly in interpretation during the last two years. However, the large amount of basic research reviewed in most of the articles is of great value to the reader interested in the thorough investigation of this subject.

**Surgical Pathology.** By William Boyd, M.D. Sixth edition. Price \$10. Pp. 858, with 530 illustrations including 22 in color. Philadelphia: W. B. Saunders Company, 1947.

The ARCHIVES is glad to welcome this edition. The book first appeared twenty-two years ago and ever since has reappeared in new editions every four or five years. During its life, its size and price have remained about the same despite new knowledge and higher living costs, which speaks for the artfulness of its writer. Its illustrations—which reviewers always tend to compliment—have increased in number and interest.

The author believes that something can be learned from a study of surgical pathology that cannot be learned through general pathology. He defends this belief in an agreeable style that makes for easy reading. The first five editions of this particular text have been popular both with students and with their teachers. It is safe to predict that the sixth will have an equally successful career.

**Atlas of Cardiovascular Diseases.** By Irving J. Treiger, M.D. Price, \$10. Pp. 180, with 244 illustrations. St. Louis: The C. V. Mosby Company, 1947.

This folio volume contains on each right hand page roentgenograms, electrocardiograms and photographs of gross specimens and on the left an abstract of the case history. The material is well selected and concisely presented, and the entire range of important cardiac lesions is covered. The cuts are for the most part well reproduced. The book is an excellent summary of cardiac disease and should also be useful for quick reference.

**Dentistry: An Agency of Health Service.** By Malcolm Wallace Carr, D.D.S. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, \$1.50. Pp. 219. New York: The Commonwealth Fund, 1946.

This book is interesting reading. It contains many facts concerning dentistry presented in a clearcut, brief and concise manner. It would serve an extremely useful purpose in public and high school libraries, in which young men and women interested in professional education might have access to it.

**Principles of Hematology.** By Russell L. Haden, M.D. Third edition. Price, \$5. Pp. 366, with 171 illustrations. Philadelphia: Lea & Febiger, 1946.

The third edition of this book, like the others, presents to students and clinicians a readable and helpful presentation of the clinical aspects of diseases of the blood. It has been rewritten in part and now includes a section on the technic of bone marrow puncture and a description of the findings. It continues to be a most helpful clinical text.

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